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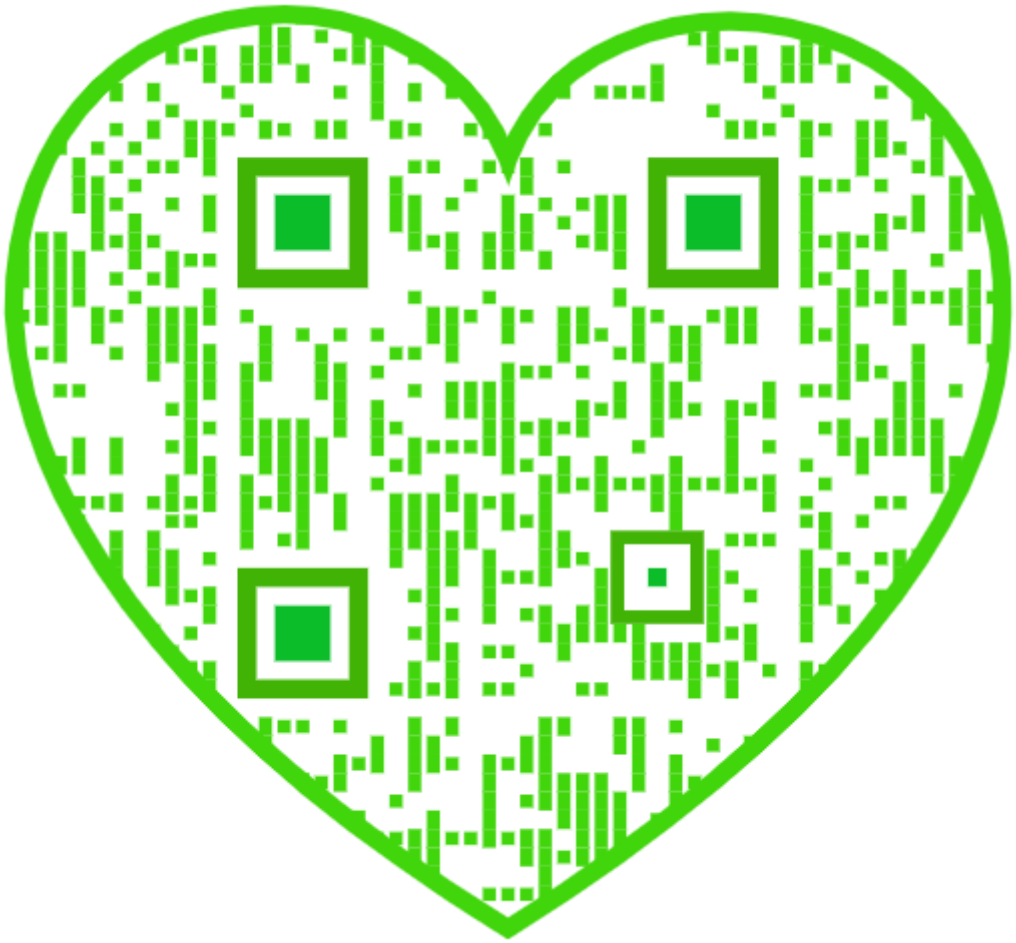

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CANCER

ITS NATURE, CAUSES, DIAGNOSIS AND TREATMENT

BY

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PREFACE

The views expressed in this volume are the results of the labors of a surgeon and a physiological chemist, working together for the past few years. The chemical work has been done by John A. Killian, Ph.D., Pathological Chemist at the House of Calvary for Cancer, and formerly Instructor in Physiological Chemistry at Fordham University. No attempt has been made to settle definitely many of the questions arising in connection with this wide-spreading disease, but an effort has been made to show the lines along which future investigators probably must work. In addition, the result of the labors of the authors is presented, both as to methods of diagnosis which they have found useful, and as to principles and details of treatment, the carrying out of which may ameliorate some of the suffering and at least often retard further progress for a considerable length of time.

We wish to thank the following individuals for valuable aid rendered us in the prep-

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PART I

CAUSES OF CANCER

CHAPTER I

Etiology of Cancer

In the whole field of pathology there is no problem at once more essential and more baffling than the disclosure of the causes inciting and promoting the growth of tumors of all kinds. The question of the origin of the unchecked proliferation of cells and the transmission of the resulting neoplasms to foreign hosts has occupied the minds of experimentalists and clinicians as well for centuries, and although a number of ephemeral theories have been proposed, at the present day we are as ignorant of the etiology of cancer as we were when the study first began. It is to be lamented that many investigators, far from adding to our knowledge upon this subject, rather have introduced confusion by the invention of new nomenclatures and

the adoption of complicated classifications. However, it is not our purpose to enter into a lengthy philosophical discussion or speculation upon fantastic theories of tumor etiology, but rather as a working basis for the clinicians to point out the salient features in our conception of the cancer process and to emphasize those factors which we believe predispose to malignant tumor formation.

In the production of a malignant neoplasm there is a combination of factors of two kinds, the predisposing or intrinsic factors and the exciting or extrinsic factors. Concerning the nature of these intrinsic causes we have at most only hypotheses to offer. No individual theory, not even a combination of them all, offers an adequate explanation; but inasmuch as each contains some truth of value to the clinicians, they merit serious consideration.

Intrinsic Causes

Cohnheim's Theory

According to Cohnheim, the malignant neoplasm has its inception in groups of cells that have become arrested in the development of the fœtus. These cells maintain an embryonic character and do not enter into the

composition or the functions of adult tissues. They are therefore called embryonic "rests." Malformations in the development of the human body are of frequent occurrence, *e. g.*, moles, clefts, nævi, etc.; and it has been the experience of every observer that these defects are more frequently the sites of malignancy in later years than the normal adult tissues.

It seems logical to assume, therefore, as Cohnheim does, that there may exist congenital, microscopical defects in the formation of tissues, *i. e.*, certain groups of cells become arrested and isolated in development, forming "rests." Every mature cell has a twofold purpose, (*a*) growth, (*b*) the performance of some specific form of work, *e. g.*, secretion, contraction, etc. Since the cell rests do not mature, they have but one form of activity—growth. These cells may remain quiescent in the tissues of which they were intended to become a part, or they may be transported to other portions of the body. Throughout this period of quiescence the cells maintain their vitality undiminished, but upon the intervention of an exciting cause, *e. g.*, irritation, inflammation, etc., they are incited to an unrestricted proliferation pro-

ducing a malignant tumor. It is difficult to understand why the tumor lies latent for so many years. The most probable explanation is the following: During health the activity of the neighboring cells of the tissue or organ hold the embryonic "rests" in abeyance; but when the functions of the tissue or organ become hampered by injury, inflammation or senility, the normal cells enter upon a retrogressive process, and the dormant "rests," no longer constrained, but still possessing their embryonic vigor, begin a process of growth, paralleled only by that of the embryo.

Every clinician will find many of his observations in accordance with this theory. It is most frequently after the menopause that carcinomata develop in the uterus and breasts, and in a large majority of cases of malignancy of the stomach a previous history of gastric ulcer of alcoholism can be obtained.

There are, on the other hand, many weak points in Cohnheim's hypothesis. It necessarily must assume a widespread distribution of cell "rests" if a group of cells is to be present wherever a form of irritation may be encountered. Moreover, this theory alone fails to account for the essential characteristics of a malignant neoplasm—its atypical

growth and the formation of metastases. Although many tumors are fœtal in character in the human body, the existence of dormant embryonic cells has never been demonstrated.

Ribbert's Theory

In common with Cohnheim's hypothesis, Ribbert ascribes the origin of a malignant tumor primarily to an isolated group of cells. However, according to the latter authority, the process of isolation is attributed not to any defect in the development of the cells themselves, but rather to an atypical development of the subjacent connective tissue. The initial stimulus, then, to tumor formation is an hyperplasia of the connective tissue, induced by trauma, irritation or chronic inflammation, which severs the original physiological connection of a group of epithelial cells from their neighbors in the same tissue or organ. Thus isolated, these cells are no longer subservient to the common cause of the tissue or organ, but they are still imbued with an embryonic capacity for growth, and if the check upon growth is removed by diminished resistance, they proliferate at will, thus producing a malignant neoplasm.

Of interest to the practitioner are these points in Ribbert's hypothesis:

(*a*) The process of "rest" isolation may be post natal as well as fœtal, *e. g.*, in the healing of a wound or in the disturbance of physiological connection of a portion of a tissue or organ in a surgical procedure.

(*b*) There exists a precancerous stage: *e. g.*, a chronic dermatitis may be a precancerous stage in the formation of an epithelioma. Or in the development of carcinoma of the tongue there will be a pre-existing subepithelial reaction.

(*c*) Tumors are unicentric. They progress by the division of their own cells, and there is no transitional zone between the tumor itself and the normal tissue. It may invade and thrust apart the surrounding cells, but it does not convert them into tumor cells.

Ribbert's theory, however, does not coincide with facts of common knowledge. According to this hypothesis a condition most favorable to the production of a tumor would be the healing of a wound; but a malignancy in this condition is very rare. Moreover, in skin grafts a proliferation of tissue has never been recorded.

The Parasitic Theory

In a certain biological sense every neoplasm is a parasite, for it lives and grows at the expense of another organism—its host. It is not, however, with this significance that we speak of the parasitic nature of cancer. The earliest observers ascribed the origin and the propagation of the disease to microorganisms, and even at the present day a few authorities adhere to that view of cancer formation.

The theory of the parasitic origin of malignant tumors is not without some foundation. Although it is not uncommon to find bacteria in and around malignant growths, there is no evidence to connect their activity with tumor formation. We must always bear in mind the fact that the *ulceration is not the cancer*, but that in the vicinity of a malignant neoplasm the natural protective powers of the tissue cells are inhibited, and therefore the site of a malignancy becomes a fertile field for bacterial growth.

One of the authors has had the opportunity of following several cases of cancer that received *B. Prodigiosus* vaccine. One of these cases, in which the site of operation did not heal following the removal of a tumor

from the abdomen, manifested no improvement. In the other cases of epithelioma with superimposed suppurative processes, an apparent improvement in checking the progress of the infection was observed. This improvement must be attributed to a stimulation of antibody formation in the blood of the host which enabled the host to ward off the infection, but not the neoplasm. All the cases, however, terminated fatally.

Minute bodies, of an intracellular or an extracellular type, with staining properties essentially different from the tumor cells, have been demonstrated about cancerous growths. Some authorities, as Russel and Romcalli, have considered them blastomycetes, while others look upon them as intracellular protozoa. It has been found, however, that their occurrence is not confined to malignant neoplasms, but they also frequently accompany inflammatory conditions. It is generally agreed now that these bodies are products of the cell metabolism suspended in the cytoplasm or extruded into the intracellular spaces.

The all-important and much mooted question of the infectivity of carcinoma and sarcoma depends upon the substantiation of their

parasitic origin. That there is a strong popular conviction of the possible transference of the disease from one person to another is evident to everyone experienced in history-taking among patients of this type. The onset of the malady will be dated from and attributed to actual contact with an affected person, as in the dressing of a cancerous patient, or the use of the same dishes or drinking cups. If carefully examined, it will be found that with the exception of a few striking coincidences, the greater part of these histories will not bear scrutiny. On the contrary, we possess the more reliable evidence that there is no instance on record of an infection among nurses, clinicians or pathologists, nor do they possess an undue liability or immunity toward cancer. The only evidence conclusive of the existence of a parasitic micro-organism as the causative agent in the production of cancer would be the actual demonstration of the microbe invariably present in tumors and capable of producing histologically identical growths when transmitted to other hosts. The lack of such evidence, however, leaves the question an open one. It is indeed true that all types of micro-organisms, cocci, bacilli, blastomycetes, protozoa and metazoa, have at

one time or another been associated with the etiology of cancer, and in fact the variety of these alleged causative agents, far from convincing, has rather increased our scepticism. For a time the *Micrococcus neoformans*, described by Doyen, received more serious consideration than the others. The *Micrococcus neoformans* is closely allied to the *Staphylococcus albus*, and, according to Doyen, is invariably found in the vicinity of new growths, and animals experimentally inoculated with the coccus develop malignant neoplasms. Later workers, however, have not only failed to isolate the organism from malignant tumors, but they have shown that many tumors are sterile.

There can be no question but that certain parasites, such as metazoa, play an important rôle in cancer formation, but their causation is rather secondary than primary, *i. e.*, one of irritation. We can conceive of a chronic irritation due to a parasitic infection, stimulating a latent malignancy in an organism where the primary cause, *i. e.*, predisposition, was previously active. But the influence of the parasite in such a case is in no way analogous to the part taken by the tubercle bacillus in the production of tuberculosis.

The results obtained in the experimental production of cancerous growths have demonstrated beyond a possibility of doubt that for the successful transference of a neoplasm from one host to another the intact cancer cell is essential. Attempts to inoculate animals with products of the cancer cells, or with parasites isolated from the growth, have invariably failed. If, therefore, a specific organism does exist, it must be essentially different from all micro-organisms within the scope of our present knowledge. In view of the evidence afforded by clinical observations and experimental study, we must not regard cancer as a parasitic disease in the accepted significance of that term. There is then no possibility of infection save by inoculation with the living cancer cell. Further, although the ulceration is not the cancer or the cause of it, there is every need of keeping the growth aseptic by agents described in a later chapter, if we are to preserve the vitality of the neighboring tissue cells and to assist their protective forces.

The theories so far discussed are not individually sufficient to account either for the formation, propagation, or the transmission of malignant growths. All of them have

many good points; so, too, all of them have their weak points. It will be noted that they bring into consideration the pathology of malignant tumors. In fact this might be expected when we recall that their authors were pathologists of the old school, who considered nothing worthy of consideration unless it could be shown under the microscope. However, with the recent advance in the chemistry of living organisms, many facts have been brought to light that have revolutionized our conception of the factors influencing the development of pathological conditions. Recent investigations in the composition of the blood and the other body fluids, in patients suffering from carcinoma and sarcoma, have demonstrated that these fluids differ widely from the composition of normal fluids. It will be observed, as stated in a later chapter, that the blood of patients suffering from malignancies shows an increase in non-protein nitrogen, as well as an increase in non-protein sulphur. Our own investigations have shown that this increase in the non-protein and non-oxidized sulphur, continually known as neutral sulphur, shows also in the urine. It is also mentioned by Greenwald, "Increase in sulphur in Urine," *Journal of Cancer Research*, 1917.

There are two possible exceptions to the occurrence of the abnormal amount of nitrogen and sulphur in the blood. They may be due to the presence of a combination which we call toxemia, being both nitrogen and sulphur, but differ from the ordinary compounds with which we are familiar in the blood, as urea and so on. The presence of this toxemia may incite epithelial cells or connective tissue cells to an unrestricted proliferation. It may be that these cells are isolated from their neighbors, as rests, as Cohnheim thinks, but the exciting cause would be the presence of this compound or compounds detected by the increase of nitrogen and sulphur in the blood stream. It is interesting to note in this communication that Jacques Loeb has recently shown that unfertilized ova may be incited to greater and more mature development by the agency of certain chemical substitutes. In an analogous manner the presence of this compound or compounds in the blood stream may incite cells to unrestricted proliferation. On the other hand, the compound containing this nitrogen and sulphur may be a product of the metabolism of the carcinoma or the sarcoma, which finds its way into the blood stream. If this latter

view be true, then the metabolism of the malignant cells varies from the metabolism of healthy cells, because in the latter case we find as metabolic products, urea, creatinine, and uric acid. The compound indication of the presence of the malignancy is none of these three. No matter what our conception of the nature of a cancer may be, the fact remains that its presence in the organism is attended by an increase of the non-protein nitrogen and sulphur, and this fact is most valuable in diagnosing a latent malignant tumor or in differentiating a malignant from a benign tumor.

CHAPTER II

Heredity

The subject of heredity in connection with malignant growth is such an important one, and one which at the present time is attracting so much attention, that we feel obliged to mention it, although our views concerning it are not so well fortified but that they are subject to modification in the future as a result of the publication of investigations that are being carried on at the present time by workers in this field.

If the human organism reacted to disease in exactly the way that certain animals do, such as mice, we would be justified in holding the same conceptions concerning the nature of this disease as are held by Miss Maud Slye, of the Ortho Sprague Institute, Chicago, the results of whose researches have been published from time to time in the *Journal for Cancer Research* during the years of 1916 and 1917. Her results seem to show that mouse cancer is transmissible exactly ac-

cording to the laws of the so-called "Mendelian Theory." This theory was first promulgated through work on peas by Gregor Johann Mendel in 1866, and within the last ten years has attracted much attention. The most exhaustive of many works on the subject, and one to which we would call attention, is that by Bateson, published in 1913. The theory can be perhaps more easily illustrated by giving the results of some investigations on Andalusian pigeons, results which correspond with the work done by Mendel on peas. If fifty white and fifty black Andalusian pigeons are mated, the result would be one hundred blue pigeons. If these blue pigeons, which are the second generation, are mated among themselves, the result in the third generation will be twenty-five white, twenty-five black, and fifty blue pigeons. The twenty-five white would breed true to white, the twenty-five black would breed true to black, and the fifty blue would continue to breed the following generation in the same proportion, one-half blue, one-quarter white, and one-quarter black.

Quoting from the Catholic Encyclopedia under "Mendel," the results of his work on peas were as follows: "In the case of the pea,

he observed that some were tall, some dwarf in habit; some had round seeds, others wrinkled; some had green endosperm, others yellow. For the purpose of his own observation he selected seven such characters and studied their behavior under hybridization. From what occurred he was led to believe that the progeny of the various crosses behaved in regard to these characters not in a haphazard manner, but in one which was reducible to the terms of a so-called "Natural Law." One instance given by Bateson will explain what happens: there are tall and short (or "Cupid") sweet peas, and in them we have plants showing a pair of marked and easily recognizable opposite characters. The tall and short forms are crossed with one another, and the seeds are collected and sown. The resultant plants will be found to belong entirely to the tall variety, which has apparently wiped out the short. If, however, this generation of seeds is sown and the flowers of the resultant plants be self-fertilized, the result is that, when their seeds are sown and have sprung up into plants, it is found that these are mixed, and mixed in definite proportions, for on the average it will be found that there are three tall forms for every one

of the short. It follows that the dwarfishness was not wiped out, but that it was temporarily obscured in the second generation, though present all the time potentially. To the character which alone appears in the first cross is given the name *dominant* (in this instance tallness is dominant) and to the hidden character that of *recessive* (dwarfishness in the example). When the talls and dwarfs of the third generation are allowed to be self-fertilized, it is found that all the recessives (dwarfs) breed true, and what is more, will go on breeding true as long as uninterfered with. Not so with the dominants which, after self-fertilization, produce both talls and dwarfs. Some of the talls of this generation will breed true and continue to breed true; others will not, but produce a mixed progeny. Hence, out of the first plants, seventy-five will be talls (dominants) and twenty-five dwarfs (recessives), these last being pure. Of the seventy-five talls, twenty-five will be pure and will go on producing talls; fifty will be mixed, and their progeny will consist of pure dominants, mixed dominants, and recessives, as has been stated above."

As we have understood the work done by the investigator in mouse cancer, previously

referred to, transmission of cancer in mice follows out Mendel's laws along the lines above mentioned. And not only does it seem true about mouse cancer in general, but certain types of cancer in them, like cancer of the liver (by proper mating of the mice), seem to develop according to Mendel's laws.

We are inclined to believe that, as regards human beings, statistics so far are unable to demonstrate any such conditions as those in the mice above referred to, but it is one of those matters that time and proper study of cases and their classification will finally clear up.

Somewhat generally speaking, there seems to be no doubt that a tendency to cancer exists in some families; and if this be true, as we believe it to be, we may also recall the physiological suggestion referred to in other chapters, that a toxin may pass from the placenta to the fœtal circulation, predisposing the fœtus to a malignant formation at the intervention of the secondary cause. It appears to us that, if cancer is inherited, the geographical history of cancer should have some bearing on the subject, and to some extent we have carried on investigations of our own in

this direction, although not enough to have derived from them alone positive conclusions. Investigations as to the character of disease on an island (Pitcairns Island), which is so remote from civilization that mixture of foreign blood has practically never been introduced, shows that cancer has never been seen. This is on the authority of Miss McCoy, a trained nurse, a resident of the island, who recently visited this country.

On some other small islands, not far from each other, in the West Indies, but not so much isolated, there is a large mortality from malignant growth, while in the neighboring island it is very small.

The above data, while not conclusive, and not definite enough to be of much scientific value, strengthen our views as to the part played by heredity in cancer. This, combined with what we have been able to find out about the animal transmission as mentioned above, with the knowledge we have of the transmission of other diseases resembling cancer, backed up with our clinical experience—while the exact method, the exact proportion, or the exact laws governing such transmissions in human beings is still a subject to be definitely settled in the future—have given us a

very positive belief that there exists a hereditary tendency to cancer transmission; but with the exact physiological and anatomical laws governing these we are not as yet familiar.

PART II

NATURE OF CANCER

CHAPTER I

Nature of Cancer

We wish to make it clear that, in this chapter as well as the preceding ones, we have no desire to overload this little volume with material which can easily be obtained by those particularly interested in the subject, more fully from many of the more recent works, written by men more familiar than ourselves with the pathological and histological technique; but it has seemed wise to call attention to the conclusions most generally accepted at the present time, hoping that by such means this book may be more of an aid to those interested in the diagnosis of cancer who may not have the opportunity to obtain this information or are not already conversant with it. At the same time it helps to make clear any theories of our own we have desired to publish and enables us to present the results of

any original work which we have done in a somewhat more suitable setting.

Cancerous growths partake of the nature of tumors, and hence a discussion of the characteristics of tumors from a pathological standpoint will be essential before we can consider the minute structure of cancerous growths. Powell White has defined a tumor as a mass of cells, tissues, or organs, resembling those normally present in the body, but arranged atypically, which grow at the expense of the organism, without at the same time subserving any useful purpose in the host. This definition most satisfactorily fulfills all the conditions noted by pathologists or surgeons in connection with tumors in general. All tumors are derived from preexistent cells of the body, which they resemble more or less closely. However, in certain conditions the characteristics of the cells may revert to a primitive form so that they no longer resemble the cells of the tissues from which they were derived. Hence their origin is defined. Tumors whose cells preserve the characteristics of the original tissue or organ are called typical growths, but where the original characteristics of the parent tissue or organ are lost the growth is

spoken of as atypical. All tumors are composed of two structures, a matrix or stroma, and the parenchyma or the tumor cell proper. It is the nature of the parenchyma that gives the tumor its distinctive features. In various tumors a wide variation in the relation of the parenchyma to the stroma will be noted. The general statement may be made that benign tumors are typical. In malignant tumors, on the other hand, the cells differ considerably from the parent cells. There is noted a reversion to the embryonic or vegetative form of cell, and this reversion is spoken of as anaplasia. There exists a close relationship between the histological structure of the cell and its pathology. That is to say, in innocent tumors the cells which still preserve the morphology of the parent may continue to perform the functions of the organ or tissue from which they were derived; but, on the contrary, in malignant tumors where a variation from the prototype occurs, all functions are lost except that of growth. In the nucleus of the parenchymatous cells some new changes will be observed in typical growths. The nuclei are normal, but in atypical growths wide variations occur in the size or shape of the nucleus, or in multiplication, or in de-

generative changes. The most common form of variation occurs in the character of cell division; that is, in rapidly growing tumors instead of indirect cell division or mitosis we shall note particularly around the margin of the growth evidences of direct cell division or karyokinesis.

The supporting network of the tumor or its matrix is an outgrowth of the stroma from the parent tissue. It carries the vascular and lymph supply to the tumor. In the benign type the blood vessels are well developed, but in the malignant type they are capillaries, and very often consist merely of a lining of endothelial cells. The lymph supply is principally through lymph spaces. No nerves have been found in tumor stroma. Occasionally around the periphery one may find nerve tissue that has become incorporated in the tumor by the invasion of neighboring tissue. A spontaneous disappearance of a tumor or a check in its growth may occur, owing to a proliferation of the connective tissue which chokes the neoplastic elements. However, under other conditions the stroma may assume malignant characteristics and proliferate in proportion to the parenchyma. Or, on the other hand, it may undergo calcareous degenera-

tion. In innocent tumors no variation in the character of the connective tissue will be found and the parenchyma and stroma occur side by side.

The method by which tumors proliferate has been a subject of dispute among pathologists. Some authorities have claimed that the tumor cells cause a degeneration in the cells of neighboring tissue, and that this degeneration is a reversion to the type of cell in the parenchyma of the tumor. These degenerative, changes have been reported principally around the periphery of the tumor, but it has been impossible to substantiate such a claim, because what may appear to be a single tumor, on careful examination will appear to be a multiple tumor. However, the more logical view entertained by the majority of pathologists is that tumors are unicentric, that is, they propagate by expansion and infiltration. When a tumor occurs by expansion the increase in the tumor substance is uniform throughout. This type of growth is the rule in typical tumors. Malignant tumors prefer to grow by infiltration, that is, by peripheral extension, with little or no growth in the center of the tumor, in fact the central portion, deprived of its blood supply, may

undergo a degenerative change or a necrobiosis. From the point of view of the surgeon and the clinician the most pertinent classification of tumors is into groups, the innocent and the malignant. The clinician's conception of malignancy is radically different from that of the pathologist. To the clinician the growth which eventually entails a fatal termination of the host is considered malignant. The pathologist, on the contrary, classifies as malignant those tumors whose cells possess definite characteristics, and the tumor as a whole manifests properties which experience has shown to necessitate a fatal prognosis to the host. In other words, to the clinician the criterion of malignancy is the prognosis, but to the pathologist it is the properties of the gross structure and its histological characteristics. Those properties which have been found by experience to be invariably associated with pathologically malignant tumors are, first, rapidity of growth; second, the vegetative or embryonic nature of the cells; third, infiltration; fourth, the formation of metastases leading to a local recurrence; fifth, ulceration; sixth, a tendency to degenerative changes; and, seventh, the production of cachexia and subsequent anemia.

The **rate of growth** is not an invariable indication of the nature of the tumor. The general statement that malignant neoplasms manifest a rapidity of growth, while benign tumors are slow growing, admits of many exceptions. A slow-growing tumor is not necessarily innocent. Sarcomata, however, are almost invariably rapid in growth. Microscopically, this rapidity of growth is indicated by a peripheral invasion of adjacent structures and in the peripheral cells there will be noted numerous points of mitosis. The growth of the malignant tumor is independent of the physical condition of the host.

Character of the Cell.—It was noted above that cells of malignant neoplasms manifest a tendency to a reversion to the primitive type, and this reversion has been called by Hausemann "anaplasia." For mature cells, possession of two functions is necessary: (1) of growth, and (2) the performance of some specific work, *e. g.*, secretion, contraction, and so on. When such a cell undergoes a process of anaplasia its specific function is lost, and all the energy within the cell is expended in unrestrained growth. Microscopical examination of cells will show evidence of the performance of their specific work, as, for in-

stance, the cells of mucous membranes will be observed to contain mucin, and this mucin occurs in the cytoplasm, and frequently gives the cell a goblet appearance. When anaplasia takes place, the cytoplasm will be seen to have diminished. The goblet appearance of the cells is no longer noted and the nuclei are relatively larger than under normal conditions. It must be borne in mind, however, that a diagnosis cannot be made upon changes in one cancer cell, but an examination of the tumor as a whole must be made, and if anaplasia is noted to be the rule throughout the tumor, then it may safely be classified as malignant.

Metastasis.—The characteristic of neoplasms of the malignant type, which renders their removal by surgical means a practical impossibility, is the ability to form secondary growths of a similar character at a distance from the original tumor, and this characteristic is called metastasis. But metastasis must be distinguished carefully from a local recurrence. The latter is the reappearance of the malignant process in the immediate neighborhood of the original neoplasm. The formation of metastasis has been shown to be due to the spreading of intact cancer cells from

the primary focus to a distant site by a combination of three processes: first, by the lymphatic system; second, by the venous system; and third, by the arterial system. In a dissemination of cancerous cells the lymphatic system plays the most important part. Such, however, is not true of sarcomata, and most probably this is due to the fact that the characteristic cells of sarcoma, which are larger than those of carcinoma, cannot pass through the lymph walls, and consequently they are passed on to the vascular system. The carcinomata cells, however, filter out through the lymph walls before they reach the vascular system. Cells from primary cancerous growths may escape into the lymph system, where they will be transported until they become fixed, and at such point of fixation they proliferate and produce a secondary growth.

Cancer cells from the primary growth may escape into the lymphatic system. An accumulation of such cells and their fixation, with consequent proliferation along the lymphatics, may cause the formation of a series of nodules, thus producing what is known as lymphangitis carcinomatosis. On the other hand, the cells may not become fixed until they reach the first lymph glands. The pro-

liferation of the malignant cells here will give rise to growths very similar to the original tumor. In the draining of the lymph through the lymph glands we would expect the first series of glands to be involved, *i. e.*, to manifest evidences of metastatic growths. This is a very important diagnostic and prognostic sign. Almost invariably, in cases of malignant neoplasms, secondary tumors will be found in the lymph glands that are the first to receive the lymph from the neighborhood of the original tumor. When, however, the invasion has extended beyond the first to the second series of glands, then the case must be considered inoperable. Thus, in a case of malignancy of the forearm, the first glands to show metastatic growths will be the glands of the antecubital fossa. However, if the glands of the axilla also are involved, we must consider the dissemination of metastases too widespread to be relieved by surgical intervention. The primary function of a lymph gland is to check the spread of infection by draining infecting agents from the lymph stream, thus preventing them from entering the vascular system. The lymphatics can check cancer only for a time, and when the cells have passed the first series of glands and

have reached the second, this means that the first barriers have been passed and most probably the invading cells have entered the blood stream.

An invasion of the venous branch of the vascular system may take place in two ways, by the passage of the cancer cells from the lymph system into the veins, or by the direct invasion of the wall of the vein. In the first case numerous metastases will be formed throughout the lymphatic system and elsewhere. In the second case, when the malignant cells have found their way into the intima and have eroded this, an extension of the growth into the vein follows. If the vein involved is of any considerable size, a fatal hemorrhage is the issue. Whether the vein be invaded in one way or the other, metastatic growth will develop promptly in the lungs. It may be said that a growth manifesting hemorrhages has already involved the blood vessels, and therefore the blood stream has been burdened with intact cells that will produce metastatic growths.

An extension of cancer cells into the arterial system is less common than the invasion of the venous system. The arterial walls offer greater resistance to the invasion of the

growth. Cancer cells that primarily entered the lymphatic system are removed from the blood before it reaches the arteries. Cancer cells entering the arteries would be carried to the periphery, where they would be blocked by the capillaries, producing peripheral metastatic growths. Veins, however, carry the cells centrally. Secondary growths even from primary peripheral tumors are more frequently located centrally than in the extremities.

In the peritoneal and thoracic cavities, metastases may occur, independent of the lymph or blood supply. Thus, a cancer of the stomach may produce a secondary growth in the ovaries or rectum. Such secondary growths are due to the fact that cells become dislodged from the original growth through the movements of the viscera, or by surgical manipulation, or palpation. Such cells may be carried to a distant part of the cavity by the peritoneal or pleural fluid, and wherever they become fixed produce secondary tumors.

Our advice to the clinicians, then, is to avoid all unnecessary manipulation of tumors suspected of possessing malignant characteristics or a tendency thereto.

Recurrence.—From the point of view of

clinical medicine the salient feature of malignant tumors is their tendency to local recurrence, that is, to appear, after their removal, in the vicinity of the original growth. The fact that tumor excisions have been ineffectual in promoting permanent cures must be attributed to this property, characteristic of malignancies. Obviously it is of little value as a diagnostic sign; however, a knowledge of the means by which recurrence takes place is of inestimable practical value to the surgeon and should form the basis of his technique.

We know that a malignant neoplasm does not develop anew, but that cancer cells in a number of possible ways have been left intact in the organism and that these cells serve as a nucleus for a second tumor. The cancer cells migrating from the original tumor may have become fixed at some distance from the parent cell, and the new tumor due to these cells may be separated from the original wound by a margin of healthy tissue. As has been previously pointed out, cancer cells migrate principally through the lymphatic and venous systems.

Elsewhere it has been shown that cancer cells disseminate throughout the organism

primarily by the lymphatic system. A different growth of the primary tumor may extend into the lymphatic ducts and proliferate there, checking the flow of the lymph. In the removal of all the tissues that microscopically appears to be diseased, the cells that have permeated the lymph system may be left intact and a recurrence will follow through these remaining cells. Particular attention, therefore, must be given in surgical technique not alone to the removal of the tissue that has the gross appearance of a cancer growth, but as well as to the excision of all tissue in the neighborhood that is known to be prone to the dissemination of cancer cells, and this tissue should be removed as widely as the anatomical relations to other parts will permit. This fact must especially be borne in mind in the surgical treatment of growths in organs or tissues that have a rich lymph supply, as, for instance, the breast. By means of chains of lymphatic nodes the breast is intimately connected with the lymphatic glands of the axilla, the supra-clavicular glands, the mediastinal glands, and the glands of the opposite breast. Malignant neoplasms of the breast which show a metastasis to any of these glands may be considered inoperable. If,

however, the case is operable, not only the neoplasm, but the entire breast with the fascia and pectoral muscles must be excised to prevent a recurrence due to disseminated intact cells. Cancer cells spread likewise to the venous system. If a growth manifests evidence of hemorrhage, in all probability the growth has eroded the walls of the vein. The destruction of the venous wall entails the entrance of malignant cells into the venous blood, which means that metastases have taken place and that recurrence will follow, due to these metastases. Recurrence may be due also to cells dislodged from the primary tumor by mechanical manipulation, and this is particularly true in recurrence within the serous cavities, that is, within the thorax or the peritoneum. We cannot impress too strongly upon the physician and the patient the risk following undue handling of malignant tumors. The therapeutic measures for the relief of inflammatory processes, such as massage and rubbing, should never be employed where the tumor is suspected of being cancerous, and the examinations of such growths should be undertaken with extreme gentleness and not repeated unless absolutely necessary. Furthermore, the cancer cells may be

disseminated by incising a growth to obtain a piece of tissue for examination. At times a rapid examination of the tumor by the frozen section method may be thought advisable, although positive conclusions cannot be drawn from its results. In cases of this kind, when practicable, a piece of tumor should be removed by cautery, rather than by the knife. Authorities who have had experience in handling cancer patients with and without operations are agreed that metastases in recurrence can be checked more rapidly in patients where the tumors have not been excised or cut into for microscopical examination, than in cases that have been operated upon. It would seem, therefore, that surgical interference—if not based upon an intimate knowledge of the means by which cancer cells disseminate, causing recurrence, and of the methods of stimulating cancer cells to proliferation—is apt to be ill-advised and attended with unfortunate results.

Experimental work upon the transplantation of tumors in mice, from one individual to another, have shown that a tumor may be produced in the second host by the implantation of intact cells subcutaneously. Therefore, all that is needed to produce a second

tumor is an inoculation with the living cells. Whether cancer may be transplanted from one human being to another in a similar manner has not been proved, but statistics show that the growth may be transferred from one locality to another within the same individual. As applied to the methods for treatment of cancer, observation implies that cancer cells coming in contact with other organs will produce secondary tumors. This is particularly true of sloughing cancerous tumors. The roof of the urinary bladder is very apt to be infected from a cancer at its base. An instructive illustration of this point in connection with another portion of the body came under the observation of one of the authors recently. The patient, a man of middle age, complained of severe penetrating pain in the right epigastric region. The cause of the pain was diagnosed by the surgeon as cholelithiasis. During the operation, undertaken without a suspicion of a malignant neoplasm, a cancer was found in the upper right epigastric region. A piece of tissue was removed for examination, and the wound came in contact with the freshly incised growth. When it was known that the abdominal growth was malignant the wound was sutured and the

patient was transferred to an institution devoted exclusively to cases of cancer. A short time after his entrance a growth developed along the abdominal scar and spread very rapidly. Moreover, new vigor was apparently given to the intra-abdominal growth, which within a short time could be palpated with ease; and at autopsy it was found to have invaded the small intestines, and by pressure upon the spinal cord to have produced paralysis and complete anesthesia of the lower extremities. Further, the use of a trocar in tapping or exploring malignant tumors is invariably productive of the development of secondary tumors along the line of entrance of the instrument. The greatest number of recurrences due to implantation of cancer cells in healthy tissue are reported in the excision of malignant growths of the female genito-urinary tract. Cancer of the uterus is probably the most common form of the malady in the female sex. The removal of the tumors of the uterus by vaginal hysterectomy is frequently followed by the development of the tumor in the scar in the apex of the vagina, or the sides of the vulva (in cases of narrow vaginal orifice), when incisions are made at these points to afford more space for

the removal of the uterus. It is practically impossible to keep these cut surfaces from touching the cancerous growth and thus to avoid an implantation of the cancer cells in the vagina. The use of the cautery, however, to destroy as much as possible of the growth before its removal, although it does not obviate all possibility of implantations, nevertheless may diminish the chances of infection through contact of living cancer cells with healthy tissues.

The cells that remain in the wound after excision probably proliferate at once. However, some time will intervene before the presence of the new growth can be demonstrated. The time that must elapse without the development of a recurrence, before the case can be considered cured, differs according to different authorities. Formerly it was considered that a lapse of three years without a recurrence was indicative of an effectual cure. Other authorities have placed the limit at two years, while it is now generally accepted that recurrence may take place within five years (or more) of the operation.

Ulceration is not pathognomonic of malignant tumors, and therefore as a diagnostic sign it has little value. Innocent tumors may

ulcerate and malignant tumors may remain sterile. Malignant tumors ulcerate when they are exposed to injury or irritation, and in this mechanical production of the ulceration benign tumors are similar to the malignant.

A peripheral hyperplasia with a central hypoplasia leading to degeneration is characteristic of a rapidity of growth. A malignant tumor depends for its nourishment not upon special vascular and lymph supply to itself, but principally upon the blood vessels in the stroma of the tissue invaded. Hence the periphery of the tumor receives a rich supply of nutritive material. When, however, the blood vessels become incorporated in the growth, their tissues are invaded and destroyed, which means that the central portion of the tumor degenerates owing to a failure of nutrition. The degeneration may take the form of an active necrosis, or the form of a quiet necrosis, or necrobiosis. On the other hand, sarcomata may undergo a calcareous degeneration or a myxomatosis. In the latter case the greater portion of the tumor assumes a jelly-like appearance and is surrounded by a thin wall of tissue.

Cachexia is not invariably present, particularly in sarcomatous cases. It is a late con-

stitutional development, resulting from the effect of the tumor upon the organism as a whole. The time of the development of the cachexia depends particularly upon the location of the tumor. Thus a neoplasm of the stomach directly interferes with the supply of nourishment to the body, so that the appearance of the cachexia takes place in the earlier stages. Peripheral tumors, however, for instance, of the breast, may attain an enormous size before the patient develops a cachectic appearance, and in fact the cachexia may never take place. In peripheral tumors the factors that play the greatest part in producing the cachexia are ulceration of the surfaces with hemorrhage leading to a septic condition. Cachexia due to carcinomata that slough rapidly will develop more rapidly than in any other conditions; for instance, a carcinoma of the cervix of the uterus is characterized by its early and continuous sloughing. This sloughing may be the cause of a secondary infection producing the cachexia. It would seem, therefore, that in treating cancer patients, inasmuch as it is necessary to stimulate the vitality in healthy cells, cachexia must be warded off, and therefore all external tumors or growths must be kept from

ulcerating. This applies to any growth, whether it involves the cervix of the uterus or some skin manifestation. As to the means of preventing ulceration and secondary infection, see chapter on Antiseptics. The cause of the cachexia is either the absorption of catabolic products of the tumor growth and its consequent metastasis, or, secondarily, the interference exerted by the tumor upon the functions of the essential organs. The entrance of cancer cells into the blood and lymph system takes place early, and a general dissemination of these cells can be detected by an analysis of the blood before cachexia develops. A degeneration of the cancer growth leads to a secondary infection, and the effect of this upon the blood stream is similar to that of any infection. Our observations upon the changes in the composition of the blood lead us to believe that there are other products concerned (of which little is known), that find their way through the tumor into the blood stream, and these products may be very important factors in the etiology of the cachexia. The interference exerted by the growth upon the essential organs may be mechanical, that is, due to pressure, erosion of its walls, and so on; or it may be due to the

absorption of toxic products, elaborated by the neoplasm.

The blood changes in malignant disease take the form characteristic of a secondary anemia, varying in intensity. The production of the anemia may be attributed to a number of causes, principal among them being: (1) the action of the toxic products of the tumor upon the organs concerned in blood production; (2) secondary infection; (3) a disturbance of the organs by the primary growth or its metastases. Ordinarily the red cell count is reduced. Variations from this statement, that is, a normal count or an increased count, must be attributed to a concentration of the blood, and is not a favorable symptom. The percentage of hemoglobin is subnormal, and this may take place even when the red cell count is normal. The number of white cells, when increased, usually indicates an infection rather than any characteristic effect of the tumor. Hemorrhage and rapid growth and the formation of metastases are also important factors in promoting leukocytosis.

The cachexia is gradual and progressive. The patient assumes a straw-yellow color, which must be attributed at least to a dimin-

ished hemoglobin production or a change in the composition of the hemoglobin. The pain is not always localized in a growth of the gastro-intestinal tract, but it may partake of the nature of what Head calls "Referred Pain." Rheumatic symptoms give rise to what has been called rheumatic diathesis. When the pains are due to an ulceration in the secondary infection, they are more potent in producing pain than the growth itself, and therefore there is every need of keeping the wound clean. In non-ulcerated cases fever is usually absent, or there may be a slight increase in temperature due to the absorption of toxic products. Some of the cases terminate in coma. The majority, however, die in a condition of general cachexia.

CHAPTER II

Pre-Cancerous Conditions

The overwhelming percentage of recurrence of cancerous lesions following operative treatment is regretfully attributed by the clinician to the fact that the malignant nature of the lesion is recognized too late, and that when it comes to the surgeon it has already advanced to the inoperable stage. Hence the operative treatment of neoplasms is far from satisfactory. In this direction it can be much improved.

This tendency to recur, as we have shown elsewhere, is characteristic of a malignant neoplasm and due to its ability to form metastases. If, therefore, it were possible by analytical and symptomatic means to foretell the development of a malignancy, or the transformation of a benign into a malignant growth, surgical treatment of cancer at this stage would be attended with much greater success.

The recent advances in pathology, coupled

with the careful collection of statistics, have rendered possible this desired end. There is no phase of pathology of greater profit to the general clinician and surgeon than the study of the so-called pre-cancerous lesions. By a pre-cancerous lesion we understand not an incipient cancer, but a benign lesion or growth of the type that most frequently develops malignant characteristics. Although such a lesion, if left alone, may never become a cancer, it should be looked upon with grave suspicion by the surgeon.

We realize that in making the above statement we are simply reiterating what has been written over and over again, particularly in the publications of the last ten years; but the subject is such an important one, and is so forcibly brought to the attention of any one who studies the whole cancer problem in a serious manner, that there never seems to be any likelihood of the statement being made too often. It should also be constantly borne in mind that statements like the above refer to a lesion or lesions which are supposed to be clear and well-marked entities, and that beyond them the rest of the system is free from cancerous invasion.

Recent works, however, through new meth-

ods of technique at the present time coming into use in the X-ray laboratories, the new advances made in the chemical examination of the urine and the blood, enable us to classify these conditions somewhat more clearly than would have been possible ten years ago. They can be classified into those having external and internal lesions; they may also be classified into those where the whole system, through lack of time or opportunity or convenience, has not been as thoroughly examined and mapped out as the modern methods of diagnosis would admit. A second class in which, the presence of these lesions having been observed, a thorough and systematic investigation of the whole system has been made; and a third class, which we may be among the first to recognize, which may be pre-cancerous, in which no particular lesion either internal or external can be diagnosed, but in which there is a bad family history of the frequency of cancer occurrence, and in which is found a marked modification in the sulphur metabolism, as told by the examinations of the blood and urine. For patients of this class we should insist on examinations being made at not far distant intervals from one another, and the necessity, as far as prac-

ticable, of such individuals leading a life where the tissue metamorphosis is kept in as near a proper condition as possible, together with the administration more or less constantly of internal medication, such as the indications surrounding any individual case would seem to require. This is referred to again in the chapters on treatment, farther on. Such cases are very apt to show changes in the sulphur metabolism similar to those occurring in gout, where the nitrogen metabolism is alone affected, and in which uric acid is the prominent characteristic and the patient is treated accordingly, but in members of the class to which we refer, the sulphur and not the uric acid seems to be the element the changes in the metabolism of which are the most prominent. This, too, brings us to a consideration at this point of another element which is apparently more or less involved in the changes in the metabolism due to cancer, and that is potash. An able treatise has been written on that work by Ross, "Cancer, Its Genesis and Treatment," London, 1912; and, recently, one by Dr. L. Duncan Bulkley, "Cancer, Its Cause and Treatment," has called attention to changes in this element. It is through a desire to dwell more carefully

on investigations personally carried on by us that the changes in potash metabolism in cancerous conditions are not more frequently mentioned. We consider them of less importance than the sulphur; but later on we may publish our observations on the metabolism of potash.

Referring now to the second class—in which some lesion has been observed either externally or internally, and in which a careful examination of the whole system has been carried on—among the lesions occurring in this class may be mentioned apparent fibrous tumors of the breast or of the uterus, old chronic inflammatory conditions of the prostate, ulcers of the stomach, and on the skin or mucous membrane such lesions as frequently recurring herpes, and patches of chronic seborrhœa, or eczema. These should all be treated by excision, X-ray, or, according to conditions surrounding any given case, by proper measures, either local or general, to do away with any chronic inflammatory process that may be present.

There still remain those cases of the first class mentioned, in which chronic lesions exist which may become cancerous, but on account of various reasons it is practically

impossible for the attendant to use all the refinements of diagnosis which might in other cases be available. Under such circumstances the attendant should carry out as many of these refinements as possible, according to the circumstances surrounding any given case. The above statement is so simple that it hardly seems necessary to dwell on it, but clinical experience seems to indicate that even at the present time thorough diagnostic measures, even when available, are not employed as frequently as they should be.

To illustrate: If a small tumor of the breast presents itself, and it is impossible to obtain careful X-ray pictures taking in the thorax, the liver, the stomach, and the gall bladder, at least a careful examination can be made of the urine and the blood, particularly as regards the sulphur content, and the prognosis before operation modified somewhat according to the conditions that may be found. Even from careful examination of these not only will it be possible to modify the prognosis, but the results of such findings may often have some modifying effect upon the nature or extent of the procedures, operative or otherwise, to be undertaken.

PART III

DIAGNOSIS OF CANCER

CHAPTER I

Details of Methods of Sulphur Findings in Blood and Urine

The blood as a circulating fluid comes into intimate contact with the cells of all the tissues and organs, and between the blood and the cells there is an exchange of nutritive material and catabolic products. We would expect, then, that the products from any particular abnormality would find their way into the blood stream, and there could be detected. The blood of cancer patients shows concentration of constituents that are not paralleled by any other pathological condition. Now, gout is characterized by an increase of the uric acid content of the blood. Chronic interstitial nephritis produces an increase in the urea, uric acid, and creatinin of the blood. Diabetes, on the contrary, does not affect the

nitrogenous constituents, but is characterized by an increase of the sugar content. None of the constitutional pathological lesions thus far studied produce any effect that can be simulated by that of the malignant tumor. A malignancy in all the cases examined has produced an increase in the non-protein nitrogen, which increase cannot be accounted for by any increase in urea, uric acid, or creatinin; nor is it an amino-nitrogen compound.

Diseases of the liver that interfere with the activities of this organ will present an increase of the amino-nitrogen, owing to the fact that the liver no longer can deaminize amino acids. Further, carcinomata manifest an increase in the total sulphur content of the blood. In these conditions the proportion between the non-oxidized and the oxidized sulphur of the blood stream is disturbed with a proportionate increase of the former.

Methods Used for Analysis of the Blood

The total non-protein sulphur of the blood in non-carcinomatous conditions may be stated, from our observations, to be an average of 3.6 milligrams per 100 c.c. of blood. Now, of this total sulphur some 80 per cent to 85 per cent is in the form of sulphates.

The remainder is non-oxidized sulphur. In carcinomatous conditions the total non-protein sulphur rises to two or three times the normal figure, while the total sulphates remain at the normal level. It appears, then, that the increase in sulphur is due to an increased amount of non-oxidized sulphur in the blood, not due, however, to the proteins.

For the methods of calculating the non-protein nitrogen, non-protein sulphur, urea, uric acid, and creatinine of the blood we refer the reader to reliable text-books on the chemistry of the blood.

Concerning the urine, all *previous* investigations conducted upon the question of sulphur metabolism in cancer conditions have utilized the Salomon-Saxl reaction for neutral sulphur in the urine. This consists in converting the ethereal sulphates in the urine by boiling with hydrochloric acid into inorganic sulphates and then precipitating the total sulphates with barium chloride, the filtrate from this reaction containing the unoxidized sulphur. To the total filtrate hydrogen peroxide was added and the mixture boiled and then upon standing the precipitate was thrown down, which precipitate represented the total neutral sulphur in the form of sul-

phate. This precipitate was allowed to settle out in a conical graduated tube, and from the amount of precipitate formed a positive or a negative reaction was reported. A most conscientious and comprehensive account of this method, with a very complete bibliography of the subject, has recently been published by Max Kahn, *Journal of Cancer Research*, July, 1917.

Kahn's conclusions, as given in the article referred to above, are as follows: "In carcinoma there is generally observed an increase in the percentage of neutral sulphur in the urine. This may be ascribed to a lessened power of oxidation or to an increased destruction of tissue with the failure of the organism to oxidize the broken-down products to the sulphate (oxidized) state. The colloidal nitrogenous substances are increased in the urine of cancer patients, as well as in the urine of anemic, diabetic and syphilitic individuals, etc. It has been the experience of the author (Kahn) that the determination of this fraction in conjunction with the Salomon-Saxl test for so-called 'neutral sulphur' is of great aid in the diagnosis of carcinoma if both of these tests are positive. A negative result with either the Salkowski-Kojo

test or the Salomon-Saxl test detracts very much from the significance of the results so far as carcinoma is concerned."

Some of our own cases have also shown, in addition to the excess of neutral sulphur, an excess in the nitrogen products in the urine. But we do not consider this latter so much indicative of carcinoma as of nephritis, which may or may not be the result of the carcinoma.

Our own investigations into the sulphur metabolism in carcinomatous conditions at first were based upon the Salomon-Saxl reaction, but it was found that this reaction was unreliable, because in all conditions the hydrogen peroxide did not completely oxidize the neutral sulphur; and, moreover, it was found difficult to obtain a sample of hydrogen peroxide which did not contain an impurity that would give a precipitate with the barium chloride. We therefore adopted the Benedict method for total sulphur and the Folin technique for the total and inorganic sulphates.

Total Sulphur.—To 10 c.c. of urine are added 5 c.c. of the Benedict sulphur reagent in an evaporating porcelain dish. The mixture is carefully heated until it solidifies, and is then heated to the maximum intensity of

the Bunsen burner for ten minutes until it becomes completely black. After the dish has cooled, this black residue is dissolved in 20 c.c. of 1-4 hydrochloric acid, and 10 c.c. of 10 per cent barium chloride are added. The precipitate is filtered off in a Gooch crucible or through filter paper and very carefully washed, and the amount of precipitate is determined by ashing and weighing.

For the Sulphur.—The urine is first diluted with an equivalent amount of 1-4 hydrochloric acid. For this purpose one takes 25 c.c. of urine, and after boiling for twenty to thirty minutes, the mixture is cooled and water added to 150 c.c., then 10 c.c. of 5 per cent barium chloride. The precipitate is filtered and weighed as for the neutral sulphur.

Inorganic Sulphates.—To 25 c.c. of urine are added 20 c.c. of 1-4 hydrochloric acid and the volume made up to 150 c.c. with water. Then 5 c.c. of 5 per cent barium chloride are added and the precipitate, after at least one hour settling, is filtered off and weighed.

These methods give the compounds of the sulphur content of the urine as grams of SO_3, and knowing the total volume of urine, it is best to express the output of sulphur as the amount excreted in twenty-four hours. The

total sulphur minus the total sulphates gives the total neutral sulphur. If it is desired to divide the neutral sulphur into two groups, the easily oxidized and the difficultly oxidized group, one should take the filtrate from the total sulphates, evaporate that down over a water bath to about 25 c.c., and then add 10 c.c. of ferric chloride, and heat over a free flame for fifteen minutes. The additional sulphur obtained by this technique over the total sulphates represents the total neutral sulphur in the easily oxidized group. By subtracting the inorganic sulphates from the total sulphates we obtain the ethereal sulphates. Subdividing the neutral sulphur into two groups enables us to say whether the liver is involved in a carcinomatous condition or not. It is the function of the liver to dilute the taurine into taurocholic acid which, combined with sodium and potassium, is excreted in the bile. A lesion of the liver of such an extent as to inhibit the functions of that organ will necessarily imply that the taurine will not be synthesized into the corresponding acid, and therefore it will not be removed from the blood stream. In such a condition an abnormal quantity of taurine will pass into the urine. This will mean an increase in the

neutral sulphur and an increase in the difficultly oxidized group, whereas in carcinoma we find an increase in the easily oxidized group. Too much stress, however, should not be placed upon the distinction, because a carcinoma of any extent will form metastases in the liver and thus interfere with the problems of its function.

Urinary Sulphur.—In the chemical investigations of metabolism, workers have generally confined their attention to the nitrogenous constituents of the urine; the sulphur, however, demands equal consideration. The sulphur occurs in the urine in two forms, the oxidized sulphur, which is composed of the inorganic sulphates and the organic sulphates, and the unoxidized sulphur, composed of a number of constituents that are divided into two groups. Of the first, the easily oxidized group, cystine and potassium sulpho-cyanate are typical examples; of the difficultly oxidized group, taurine is the salient component. The unoxidized group is more commonly known as the neutral sulphur. Folin has shown that the oxidized group consists of products of exogenous metabolism, while the neutral sulphur contains the products of endogenous metabolism, that is, of tissue break-

down. The neutral sulphur, then, would be comparable to the nitrogen of endogenous nitrogenous products, as creatinine, creatine, etc. Our own experiments upon feeding patients with sulphur-containing foods and sulphur-free foods has shown that the amount of neutral sulphur is independent of the sulphur content of the diet. The urine of carcinomatous cases is characterized by the fact that they show an increase in the neutral sulphur compared to the oxidized sulphur, but the total amount of sulphur excreted is diminished. Under normal conditions, a person engaged in moderate activity excretes about 3 grams of total sulphur estimated as SO_3 in twenty-four hours. Of this, 5 to 13 per cent is composed of neutral sulphur, about equally divided between the easily oxidized and the difficultly oxidized groups. Of the oxidized sulphur the inorganic sulphates stand to the organic sulphates in the ratio of 10 to 1. *This balance between the sulphur components is disturbed in carcinoma.* The total excretion of sulphur drops to below 2 grams in twenty-four hours. The proportion of neutral sulphur is increased to from 20 to 30 per cent, or even higher, of the total sulphur. The relative amount of neutral sul-

phur is not influenced by the sulphur content of the diet. However, X-ray treatment, as long as a growth is submitted to the emanation, greatly increases the output of neutral sulphur, but this returns again to its former level when the treatment has ceased. So, too, the surgical removal of the growth is apparently accompanied by a proportionate drop in the amount of neutral sulphur excreted. With the data at our disposal we are convinced of the invariability of these findings. But, however, the data will not permit speculation at the present time, regarding the nature of the chemical changes in a carcinomatous cell the cytoplasm predominates in amount over the nucleus, and consequently inasmuch as sulphur proteins predominate in the cytoplasm we would expect an increased output of endogenous sulphur metabolic products. At the present time plans are being made for a histo-chemical study of the changes in tumor growth, and it is hoped that these investigations will throw more light upon the origin and the significance of the increased neutral sulphur output. *However, at the present time these findings have been sufficiently substantiated to constitute a valuable aid in diagnosis.*

After the removal of a malignant tumor, it has been noted that the non-protein nitrogen and the sulphur return to their normal level. It would seem, therefore, that they are directly the products of the tumor metabolism, and not products of the effect of the tumor upon the general system, as in cachexia. The exact chemical nature of the compound or compounds whose occurrence in the blood gives rise to this abnormal amount of nitrogen and sulphur is at the present time an unsolved problem, but we are justified in considering the same as a metabolic product of the tumor growth, or a toxin invading the general circulation, and thus causing metastases. It would seem, therefore, that if this product be a toxin predisposing other tissue cells or other hosts to a malignant formation, the inoculation of other individuals with the carcinomatous blood would give rise to tumor formation in the new hosts. It has been found that in animal experimentation this fact has not been substantiated. However, we must not go too far in our deductions from animal experimentations, because it has been found that animals will not always develop constitutional lesions characteristic of the human organism. Moreover, if this compound be a

predisposing toxin, then carcinomata may be inherited, in a loose sense of the word; that is, the toxin may pass from the placental to the fœtal circulation, predisposing the fœtus to a malignant tumor formation at the intervention of the secondary cause. Such a conception coincides with observations upon carcinomata transmission in breeding mice. (See chapter on Heredity.) By successive breeding with aliens, that is, with non-infected animals, the vitality of the toxin may be greatly decreased, and consequently may be entirely bred out.

CHAPTER II

Diagnosis by Chemical and Bacteriological Means

The general statement frequently made by the surgeon, that every neoplasm, whether malignant or benign, should be removed surgically, deserves serious consideration. It is indeed true that every tumor, whose surgical removal would not interfere with the functions of any vital organ, may be excised with impunity. However, inasmuch as the treatment of cancer should not end with the excision of the tumor, there is every need to carefully diagnose a malignancy, and upon a positive diagnosis to institute an anti-carcinomatous or anti-sarcomatous treatment. Many pathologists look upon neoplasms as potentially malignant, and therefore advise their removal. However, where we have an involvement of a vital organ, excision becomes impossible, and we must resort to all the means at our disposal to substantiate the existence of a malignant neoplasm. Moreover,

inasmuch as the treatment of cancer is largely prophylactic, an early diagnosis is very essential. Where the growth is not removed by surgical means, we cannot apply a means of diagnosis based upon the morphological character of the cells, but we are forced to adopt chemical, and in some cases bacteriological, methods for the corroboration of the clinical findings.

Neoplasms of the Gastric Intestinal Tract

Stomach.—The work heretofore done by pathologists and surgeons in connection with the cases of gastric cancer which have been cured, or have resulted in any considerable prolongation of life, has only been possible in those cases in which an early diagnosis was made, thus permitting a removal of the neoplasm before it had become an extensive process. In gastric conditions we are presented with the problem of differentiating a malignant neoplasm from such conditions as gastric ulcer, chronic dilatation of the stomach, chronic gastritis—conditions which in many ways closely simulate a malignant tumor.

General Considerations.—When a gastric malignancy has become thoroughly established in the general appearance of the patient, there is the appearance of hopelessness characterized by a dullness of the eye, sunken cheeks, and listless posture, with a tendency to collapse upon any physical exertion. In addition to these there will be noted a loss of weight, scaly skin, an absence of fatty deposits about the body, and a scaphoid appearance about the abdomen. The general picture resembles that of anemia, with a grayish or yellowish tan coloration of the skin. The mucous surfaces of the mouth are pale and parched. The tongue becomes heavily coated and shows well-marked fissures and papillæ, and the breath has the odor of gastric fermentation. Decayed teeth and pyorrhœa alveolaris are not infrequently found to accompany the gastric malignancy. The mouths of such patients usually contain parasites, chief among which are amœbæ and pathogenic bacteria. In the late stages of the disease edema will sometimes occur beneath the eyes. The fermentation in the stomach gives rise to a growth of multitudes of micro-organisms, which will be taken up, and on their passage through the kidney produce a secondary

chronic nephritis. Externally there may be evidence of metastases in the lymph glands, particularly in the left supra-clavicular space. Metastases in the abdominal cavity give rise to ascites, and the composition of the fluid may be characteristic of this disease. The liver may be enlarged, owing to secondary growths. Patients with gastric malignancies very frequently manifest nervousness, which in most cases is concerned with their great loss in weight, deficiency of strength, and the inability to take food.

In 6 per cent of the cases the neoplasm has been found to involve the pylorus, the antrum, and the lesser curvature. The posterior wall has been involved in about 9 per cent and the anterior wall in about 2 per cent.

Chemical Examination.—The chemical features of the gastric secretion are not sufficient to serve as a basis for a positive diagnosis, but combined with the clinical history they make an invaluable aid in establishing or excluding the presence of a malignancy.

The most salient factor of the gastric secretion in this condition is the absence of free hydrochloric acid. This, however, is not characteristic alone of carcinoma, inasmuch as it is found also in atrophic and chronic

gastritis. It has been suggested that the absence of the hydrochloric acid is due to the combination of this acid with a compound secreted from the malignant growth. From a number of cases that we have followed, it is interesting to note that very frequently the absence of free hydrochloric acid is accompanied by diminished content of the blood.

Acid Constituents.—Before an estimation of the acidity is made, the gastric contents should be filtered. For the free acidity we use 2 c.c. of the fluid titrated against N/50 sodium hydroxide with Töpfer's solution as an indicator. For the total acidity phenolphthalein is employed, titrating the same quantity of contents with alizarin as an indicator, and subtracting this from the total acidity against the combined acidity.

For the examination of the gastric contents the earlier investigators employed the Ewald test meal and the retention meal. A meal consisting of two slices of bread, unbuttered, or dry toast were given to the patient with 200-300 c.c. of fluid, water or unsweetened tea. One hour afterwards the total contents of the stomach were aspirated and the contents analyzed for the various components of the acidity, the presence of blood, and the

peptic activity. These analyses furnished the clinician with an idea of the secretory functions of the stomach. The motility of the organ was determined by giving a meal containing articles of food poorly digested, such as raisins, and twelve hours afterwards removing the total contents of the stomach. Under these conditions only an inaccurate idea of the stomach's secretory or motor powers can be secured. Moreover, these tests are accompanied by great distress to the patient, and inasmuch as these types of cases are already in a very weakened condition, we would not advise these means of chemical diagnosis. The method which in our hands has yielded the best results is as follows. The evening before the test is to be performed a duodenal tube is swallowed. The patient lies upon the left side, until it is judged that the tube has entered the stomach. Thereupon the patient lies upon his back, and then upon his right side. The following morning it will be found that the tube has entered the duodenum. This will be indicated by the golden yellowish appearance of the fluid aspirated and its alkaline reaction to congo red. Immediately before the performance of the test another tube is dropped, with the patient sitting upright.

The swallowing of the tube may be assisted by the ingestion of a small quantity of water. About 200 c.c. of water are given to the patient, and a portion of the contents of the stomach and duodenum removed by a syringe for fifteen minutes, until the stomach is emptied. The fluid thus obtained is analyzed for its acidity, enzyme activity, and for the presence of food remains or pathological constituents, such as blood or carcinomatous cells.

If the pylorus is patent, the duodenal tube will easily enter the small intestines. In cases of pyloric stenosis the duodenal tube may be dispensed with.

The Microscopic Appearance of the Retention Contents.—To obtain the retention contents of the stomach the total fluid in the stomach is removed before the giving of water. This is done by removing the contents while the patient lies upon the right side, then upon the back, and finally upon the left side. If the pylorus is not obstructed the retention contents will be clear. It may vary in volume from a few cubic centimeters to a liter; frequently portions of poorly digested food will be removed, intermixed with mucus. If blood is present the aspirated fluid will be dark brown or coffee color. Not infre-

quently a discoloration due to bile will be obtained. In the majority of cases the fluid will have a rancid odor, due to volatile organic acids. Putrefactive odors may be due to a sloughing of the cancer tissue, or the breaking down of blood, or the penetration of foreign material through a fistula. Mucus, in a tough, stringy form, containing particles of food, or the cancer tissue will be easily obtained. Where the mobility of the stomach is very low, and the free acid deficient, the food particles will be in large amounts and poorly digested.

In spite of the clinical symptoms mentioned above as regards the appearance of the patient, loss of weight and appetite, extensive cancer infiltrations of the stomach, intestines, and both are occasionally met with at operation, where the general appearance of the patient presents no difference from that of perfect health. Such cases may, however, give a history of having very recently had symptoms of intestinal irregularities of some sort, justifying the surgeon in performing an immediate exploratory operation, as the symptoms may simulate gall bladder disease or appendicitis. It would be extremely interesting to note in these cases whether sulphur

examination of the urine and blood would not show an increase in the percentage of neutral sulphur, as we believe would be the case. So far we have not had an opportunity to verify this statement. The type of case just mentioned is comparatively rare.

CHAPTER III

Diagnosis of Malignancies of the Stomach

The problem presented in diagnosis of a malignant growth of the stomach is to differentiate such a condition from an anacid gastritis that is of the interstitial or parenchymatous type and a gastric ulcer. It may be said that gastric cancer is found principally in individuals of advanced age who give no history of chronic dyspepsia. This is most probably due to the fact that a chronic dyspeptic assiduously avoids food of a quality that is indigestible, or of a quantity beyond the capacity of the gastric digestion, and therefore the irritating action of indigestible food or of chronic overeating is obviated.

Gastric malignancies are observed more frequently in individuals with the normal habitus than in individuals with a habitus enteroptoticus. The onset of the disease is more rapid and more acute than in gastritis

and more persistent than in ulcer. The pain associated with this condition is spontaneous and is found to be independent of the intake of food. It is referred to the epigastrium and is generally described as a gnawing or boring sensation. The vomiting of the stomach contents after eating is a frequent, but not always a characteristic sign.

Etiology.—Gastric carcinoma is more frequently observed in men than in women. In men the most frequent cause is alcoholism. In both sexes chronic overeating or the intake of food difficult of digestion may be a sufficient secondary cause to invoke a malignancy. In a small percentage, patients with gastric cancer give a previous history of ulcer. Trauma, particularly of the character associated with occupational diseases, may lead to a malignant formation. If the onset of the gastric affection can be definitely dated within a year or eighteen months following injury, it is safe to say that the etiological factor in this particular case was the trauma.

Gastric ulcers, if not relieved surgically or by dietetic means, degenerate, and in this degeneration assume malignant characteristics; hence, the pre-cancerous lesion that can be definitely associated with the development

of a malignancy is a gastric ulcer. (See chapter on Precancerous Lesions.)

The most frequent *sites* of gastric malignancies are the lesser curvature, the cardia, and the pylorus. It may be interesting to note that gastric ulcer also develops in these areas. Inasmuch as the only satisfactory relief of neoplasm of the stomach is surgical procedure, it is very essential to locate the position of the growth. In general, a malignancy of the stomach, no matter where its location, will be observed to have the same effect upon the composition of the blood and urine as malignancy in other areas. In connection with sulphur metabolism in carcinomatous conditions, it is interesting to note that several years ago Schmidt of Vienna adopted as a differential sign the failure of sulpho-cyanate reaction in the saliva. However, too much stress cannot be placed upon this qualitative test. A more certain diagnosis can be arrived at from a knowledge of the gastric contents.

Differential Diagnosis.—Inasmuch as gastric ulcer may be considered a pre-cancerous lesion, it is important in this connection to consider means of detecting an ulcerating process in the gastric mucosa. An ulcer of

the chlorotic type is of a hematogenous origin; *i. e.*, it is subsequent to circulatory changes, it has primarily a low hemoglobin index and a low red cell count.

The chlorotic type of ulcer is more commonly found in young girls than in other classes of patients. Ulcers of this type leave no after-effects, and no observations have been made of the degeneration of such an ulcer into a malignancy. An ulcer, however, of a mechanical origin or subsequent to a syphilitic or a tuberculous infection is to be considered liable to degeneration. Ulcers of this type are characterized by stasis of food in the stomach, a hyperacidity of the contents, and an occasional trace of blood (all types except chlorotic). The pain commonly called epigastric is referred to the epigastrium and may radiate upwards and to the back. A large number of cases of ulcers that have shown recurrence have been studied for disturbance in sulphur and nitrogen metabolism, and it has been found that they produce no effect upon the concentration of the non-protein nitrogen and sulphur of the blood and urine, until they become malignant.

The degeneration of these ulcers into neoplasms is always of the carcinomatous and not

of the sarcomatous type. Such a degeneration can be detected first by a gradual decrease in the hyperacidity of the gastric contents, and secondly when the neoplasm has become definitely established by the proportionate increase in the neutral sulphur of the urine. Inasmuch as this degeneration may take place unaccompanied by pain, and therefore without the patient's knowledge of his condition, we would recommend the study of the composition of the urine and gastric contents for some period of time following the disappearance of pain or the relief of an ulcerative condition. In a volume of this type naturally we cannot dwell too long on every minute symptom associated with these conditions, but on account of the increasing frequency with which cancer of the stomach is commencing to be found, we think it advisable to speak more fully than on some other conditions mentioned.

Gastric carcinoma may be differentiated from an anacid gastritis by the composition of the gastric contents or by the sulphur partition of the urine. Anacid gastritis, like carcinoma, is characterized by a low acidity of the gastric contents. In this condition, however, we do not find blood by chemical

methods, nor do we find lactic acid or the Boas-Oppler bacillus. Gastritis produces no changes in the body fluids, as the blood or urine, and this fact is of vast importance in differential diagnosis.

Neoplasms of the Pancreas.—The pancreas is intimately associated with carbohydrate metabolism. In this connection its chief function consists in the removal of diastase or starch-splitting enzymes from the blood and the secretion of these enzymes in the duodenum. A malignancy at the head of the pancreas will inhibit the activity of the cells, and therefore a failure to eliminate diastase from the blood into the duodenum will follow. This can be detected by an increase of the activity of the diastase in the blood and a decreasing activity in the duodenal juice; for the calculation of these enzyme activities, the procedures we have found most available are the methods for the diastatic activity of the blood and duodenal juice as described by Killian and Myers. The activity in the blood in these conditions will rise to twice the normal, with a consequent hyperglycemia. A failure to produce lipase of the pancreas will be indicated by an abnormal quantity of neutral fat in the feces. A neoplasm of the neck of the

pancreas may by mechanical pressure upon its duct restrict the passage of the pancreatic juice into the duodenum. In these cases effects similar to those noted above will be observed. By the methods at our disposal it would be impossible to localize the neoplasm to either the head or the neck of the pancreas. However, such a differentiation is of no great value, inasmuch as surgical interference is indicated in either condition. A gumma or tuberculous process inhibiting the activities of the pancreas may be differentiated from a carcinomatous growth by the fact that no conditions other than carcinomatous disturb the concentrations of the sulphur components of the urine.

Intestinal Tract.—For diagnosis of neoplasm of the intestinal tract we may depend to a limited degree upon the presence of pathological constituents in the feces. If the process is obstructional, chronic constipation will be the result. This constipation, however, may be relieved by enemas or cathartics. It will be found that the feces, principally those following enemas or cathartics, contain occult blood. The presence of blood cannot be indicated microscopically unless the neoplasm is in the rectum or sigmoid flexure.

For the detection of blood from a neoplasm higher up in the intestinal tract, we must depend on chemical means. The feces will be found also to contain considerable quantities of mucus and necrotic epithelial cells. It is in the localization of tumors of the small or large intestine that the X-ray is of the greatest value, and for the diagnosis of tumors of this region we must depend more upon the X-ray findings and the general effect of the growth upon the physical condition of the patient and the composition of the urine and the blood, rather than upon the composition of the feces. The sulphur partition in these cases is of value.

A very common affection which shows tendencies toward malignant formation is "Smoker's Patch," or leucoplakia of the tongue. It appears as a small circumscribed white patch upon the tip or margin of the tongue and is most commonly seen in excessive smokers or in individuals giving a syphilitic history. In smokers its origin is most probably due to the irritating action of obnoxious gases upon the epithelium of the tongue. If untreated it develops malignant characteristics that form metastases in the walls of the pharynx. The only satisfactory

procedure for the relief of this condition is the complete destruction with the cautery. In the development of neoplasm from leucoplakia or other pre-cancerous conditions we must recognize a predisposing cause, and whether the exciting cause be bacillary infection, trauma, or chronic inflammation, we cannot say. However, the pathologist cannot too strongly urge upon the surgeon the necessity of a complete destruction of a leucoplakia as a predisposing lesion of carcinomatous development.

(*Note.*—The normal amount of neutral sulpho-cyanate has never been determined.)

CHAPTER IV

Differential Diagnosis between Epithelioma, Syphilis, and Diseases of the Skin

In a work of this character it hardly seems advisable to devote a great deal of space to dwelling on the somewhat minor points of difference between epithelioma in its various forms and syphilis and certain diseases of the skin. Although those experienced know that again and again mistakes in diagnosis occur often, many an individual has been, and is being, operated on for cancer who is really suffering from some of the protean forms of syphilis. In our experience (based to a considerable extent upon observations made in homes for incurables) we find syphilis mistaken for carcinoma a hundred times more frequently than we find carcinoma mistaken for syphilis.

As stated above, it seems to us more fitting to devote space to a general consideration of the means at our disposal for making positive what diseases exist, than to dwell much on all

the clinical points that may present themselves to the eye alone. These latter are more carefully considered in some of the works on Diseases of the Skin, and are often graphically portrayed by means of color plates. The Wassermann reaction is not always a safe guide, because it is very often absent in old syphilitic cases. When found to be present, its diagnostic value naturally has great weight. In many cases, particularly those of suspected gumma, it is necessary to try very thoroughly, for at least a month, an intensive anti-syphilitic treatment and to observe its effects before the diagnosis between it and epithelioma can be clearly made out. It is probably wiser in such cases to resort at first to mercury in some form and the iodides, for this purpose, than to salvarsan. It may be well to note here some clinical observations which we have made. These observations are not particularly new, but it has been surprising to notice in how many cases proper precautions have not been taken to clear up doubts which might exist as to the nature of a lesion being syphilitic or carcinomatous, through the careful carrying out of simple therapeutic tests. Iodide of potash, the administration of which it is well known has such an effect in causing

the diminution of a syphilitic gumma when the system is thoroughly saturated with it, should be administered on an empty stomach, instead of after meals, as is so often done, when it has a tendency to form the iodide of starch.

Mistakes often occur in large hospitals in the proper and systematic medication of patients, often so extremely important as an aid to diagnosis in the above-mentioned conditions, unless great care is exercised on the part of the house staff and attending physicians.

Mixed treatment, containing iodide of potash as it does, should also be administered when the stomach is empty; and a very thorough course of mercury and the iodides, of months' duration, should be instituted, and the effect carefully watched (both constitutional and local) in all doubtful cases. When, after this therapeutic test, no change has been observed in the appearance of a doubtful lesion, the results of this test should not be considered infallible, but should be followed by the administration, at least twice, of old salvarsan when possible to obtain it. We have found "Smoker's Patch," when due to syphilis, and gumma of the corpora cavernosa, to be the most difficult conditions to yield

to anti-syphilitic treatment, and thereby in a doubtful case enable us to establish a definite diagnosis.

It hardly seems necessary to remark that in doubtful lesions too much reliance should not be placed upon the results of a history of therapeutic tests previously given by the individual having such lesions. The effect of hypodermic mercurial medications has not the same diagnostic value as the procedures mentioned above.

Seborrhœa and *epithelioma* may sometimes be easily mistaken. It should be remembered that almost all forms of cancer of the skin commence with lentil-shaped papules under the skin before the breaking down of the tissue occurs. Chancre, herpes, eczema, and innocent erosions may be mistaken for epithelioma. It should also be borne in mind that while an epithelioma may develop through the breaking down of near-by multiple islets, syphilitic growths have a tendency to be more multiple. This character, too, tends to distinguish it from eczema, occasionally there being some resemblance between the two, particularly when they occur on the face. The border of epithelioma is more sharply defined, and there is less infiltration. The

diagnosis of lupus can be helped by the history, the age of the patient, and the tendency toward multiplication in lupus, together with the slow growth of the latter, and the fact that it has no tendency to cause constitutional impairment. Condylomatous warts and allied conditions may sometimes simulate epithelioma, and to distinguish them from these, and any of the conditions mentioned above which may simulate them, when practical, a specimen should be obtained, and the results of the microscopical examination by a good pathologist noted.

The value of obtaining a careful history we wish to call attention to again, particularly as regards the question of heredity, which is often overlooked. It is referred to again in this work; the value of the sulphur findings in the blood and the urine are also referred to, as is the benefit to be obtained from skilful examination by X-ray pictures. The use of some or all of these latter methods helps wonderfully in doubtful cases, both in the diagnosis as well as in the prognosis, and in furnishing indications for treatment. Some of the above methods are just coming into general use, and one or two of them have practically never been tried before.

CHAPTER V

Diagnosis by X-Ray and Cystoscope

Now that examination plates by the Roentgen ray are being made more and more frequently, as they should be—not only as a diagnostic measure to show conditions affecting the bones, but as an aid in diagnosing any diseases of the heart, lungs, pleura, abdominal organs, and urinary system—their use has not only been of great aid in the diagnosis of any given case, but is tending to alter to a great degree our conception of the nature of the disease. This is true of malignant diseases more than any other. The surgeon is no longer in the position concerning such operations as, *e. g.*, cancer of the breast, that he was only a very few years ago before the examination of the chest by the Roentgen ray became such a matter of routine. Naturally the conditions shown in the plates, such as the presence or absence of enlargement of the glands at the base of the lungs, single or multiple, indications of tumors in the pleura,

mediastinum or esophagus, probably above all, peri-bronchial thickening, together with other diagnostic evidence, among which may be mentioned the amount of unoxidized sulphur in the urine, have in a given case an effect in modifying the decision as to whether an operation is to be performed or not, also the character, and above all the prognosis in any surgical measure undertaken. In the interpretation of any plates it is hardly necessary to insist that the most careful consideration must be given to the proper interpretation of the shadows, and the testimony furnished through their use should be considered only in connection with the testimony furnished by other diagnostic factors in any given case. Naturally the co-operation of the attending surgeon and the radiographer is most important. This is particularly true in plates in which the shadows are as distinct as those of the bones, for, aside from trauma, so many other conditions may affect the bones, either the periosteum, the surface, or their centers, that mistakes may very easily occur. In our own work we have found that the appearance of dead bone shown on a plate, without other factors to account for its presence, is very indicative of being secondary to some constitu-

tional disease, of which the primary focus or foci is in some other organ of the body, and which it is often extremely difficult to locate. To illustrate further, we have noticed hypernephroma of the kidney so small as not to cause enlargement of that organ, cause necrosis in the pelvic bones and sternum, without giving rise to indications of kidney disturbance.

Syphilitic and malignant diseases of the bone are often difficult to diagnosticate from one another. Generally speaking, syphilitic growths of the bone are apt to be smaller, more nodular and numerous than malignant growths. Malignant growths of the bone are more apt to be secondary to a primary focus in some other portion of the body. Sarcoma causes more of an expansion of the bone than cancer. The age of the patient and other factors often aid in the diagnosis. Sarcoma occurs more often in the periosteum or endosteum than cancer. In the lung, primary cancerous growths are rare. The shadows given by them are not always clear; they may be taken for aneurism. They are, however, occasionally met with both in the lobes and in the hilus. Those in the lobes generally give a shadow fairly clear, with a line of demar-

cation. They can be differentiated from pneumonia by the clinical history. They give a more definite outline than tuberculosis, and there is less apt to be evidence of involvement of the lung. When they occur in the hilus they are apt to confine themselves also to a lobe. Secondary cancers are found in a nodular form, and a diffuse form as well. Neoplastic nodules can be easily made out by the plates and differentiated from tuberculosis, as they give no evidence by the stethoscope, and are quite characteristic. In diffuse form they are apt to occur at the bottom of the lung, and either cause an extension into the pleura or, on a plate, present an appearance of an épanchement pleuritique. If confined to the lung alone, these diffused secondary growths generally give no symptoms on auscultation, if the pleura is not involved; but very often these cases are mixed up with a true involvement of the pleura.

One factor also to be considered here is the negative value of these plates when the pictures are carefully taken by a competent radiographer. The mediastinum is clear, the pleura casts no shadows, and no nodules can be made out around the bronchi, which is good evidence that metastases have not as yet

taken place. It should be noted that these nodules are small, and when the mediastinum is affected it is difficult to have the discernible shadows appear. The small nodules around the bronchi are easier to be made out, as is also the thickening of the pleura, which casts a denser shadow than when due to simple pleuritic effusion of liquid, although it should be remembered that the cancerous invasion of the pleura in itself may give rise to association with effusion.

Malignant growths of the esophagus, if of any size, after the administration of bismuth, are shown clearly on a plate. Radiography of the esophagus is too often overlooked, and malignant growths are frequently not diagnosed by this measure until they have existed for a considerable time and become of quite a large size.

It is rather beyond the plan of this volume to give more than a general outline of the technique necessary to bring out all the diagnostic points that may be found in connection with the examinations of the stomach by radiography; reference is made to the last edition of Knox's "Radiography, X-Ray Therapeutics and Radium Therapy," published by Macmillan, as to the details of such

procedures as the administration of the opaque meal, bismuth, the position of the patient for examination, and interpretation of the shadows found. He states, quoting Holzknecht, that a simple ulcer of the stomach is rarely seen, although it may be suspected from the absence of shadows, indicating the passage of food through the pylorus. In malignant disease involving the lesser curvature and spreading through the pylorus, the latter point is more or less fixed and held higher up than usual; food may be seen passing through the stricture; a sharp and persistent angle or irregularity in the pyloric region is generally indicative of malignant stricture; finally, a shadow of the growth may at times be seen on the radiographs.

Malignant diseases may occur anywhere in the stomach. It sometimes shows on the plate by giving a ragged or irregular shadow, irregularity being due to the projection of the growth into the bismuth food; generally also a characteristic picture of stasis is presented. The abnormal conditions of both the small and large intestines following the bismuth meal can either be differentiated by, or else valuable testimony obtained from, the X-ray examinations. Most abnormal conditions of

the intestines present a picture of stasis, to a more or less marked degree. Kinks may be occasionally made out by this measure, and as regards the duodenum, sometimes an ulcer, if deep, can be differentiated.

Examination of the urinary tract may be performed by means of the X-ray pictures alone, through the use of the X-ray in connection with a metallic ureteral catheter, or following an injection of some salts of silver or thorium into the pelvis of the kidney, and rarely by an injection of some bismuth salts into the bladder.

Just here it is only desired to mention the value of the X-ray for diagnostic purposes when used in showing tumors of these organs. When used alone, without the other aids just mentioned, it is doubtful if a positive diagnosis of tumor of the kidney can be made by the use of the Roentgen ray unaided. In skilful hands, however, a shadow can be presented which will demonstrate if any enlargement of the kidney exists, while the density of the shadow given may at times aid in rendering positive a diagnosis of tumor.

Where examinations of the urinary tract are to be made, great care should be used to see that the intestines are thoroughly emptied

of their contents before the picture is taken, so that intestinal gases may not give rise to shadows; and where one kidney is examined, a picture of the other one should always be taken.

The value of the cystoscope as a method of diagnosing malignant growth is naturally confined to those growths occurring in or associated with the bladder. Through the use of the cystoscope, where it is suspected that a malignant growth of the kidney exists, not infrequently the ureteral catheter can be passed through the ureter to the kidney, and through that enough solution of thorium, collargol, or argyrol introduced, and an X-ray picture taken. The plate will show the shape of the pelvis and the kidney, and in that way may, in connection with other indications, give a fairly correct view as to whether a tumor of the kidney exists or not. The inability to pass the ureteral catheter in skilled hands indicates the closing of the ureter, and if a waxed tip ureteral bougie, or some other form of metal ureteral bougie, fails to indicate the presence of stone, testimony is furnished that tends to strengthen the diagnosis of some form of tumor. Very frequently, where a suspected growth exists in the kidney or ureter, it is

better to do an exploratory operation than to run the risk of misleading diagnosis or of irritation of the pelvis of the kidney through the passage of the ureteral catheter. Concerning this subject, reference is made to Greene and Brooks' "Urinary Disease and Diseases of the Kidney," 4th edition (W. B. Saunders Co., 1917), or to Braasch's "Pyelography" (W. B. Saunders, 1917).

It is in the bladder, very naturally, that the cystoscope is of such value in demonstrating a growth. Unfortunately, many of these tumors of the bladder are associated with a large prostate, so that the cystoscope cannot be passed. When it can be, an exploring cystoscope in the hands of any one that is skilled in its manipulation will, under ordinary circumstances, give a fairly clear picture of any abnormal lesion on the bladder walls.

Just here, however, it is necessary once more to return to the consideration of the resemblance between various forms of syphilitic tumors, or ulcerations of the bladder, and other ulcerations or growths, either malignant or benign. Syphilis of the bladder was never recognized as a definite entity until the cystoscope came into common use. Some of us had recognized and written about syph-

ilis as affecting the bladder, particularly as a cause of contracted bladder, from clinical observation alone. (See reference in earlier editions of Greene and Brooks, *ut supra.*) But even now these conditions are being classified, and very little has been written concerning them in English. Syphilis attacks the bladder, somewhat generally speaking, in three different forms. In its earlier stages it attacks the bladder, causing numerous small ulcerations, somewhat resembling those of mucous patches on the tongue and mouth. In the later stages the ulcerations are smaller in number, but are apt to be deeper and of a polycystic character; and in its still later stage it gives rise to gumma of the bladder. These gummata of the bladder have a characteristic appearance, and, having once been seen, are more easily recognized than described. They are very well illustrated in the colored plates of an article by G. Gayet and E. Favre, *Journal de Neurologie*, July, 1914, and have been redrawn in black and white and published in the 4th edition of Greene and Brooks (*ut supra*). They sometimes, in a rough way, resemble a bunch of grapes, also sessile tumors or pediculated tumors, being papillomatous in shape. The later ulcer-

ations of syphilis of the bladder may be mistaken for tuberculosis of the bladder when viewed under the cystoscope, and probably often have been so mistaken. Gummata of the bladder undoubtedly have been and are being mistaken either for malignant growth of the bladder or for benign bladder papillomata; and in all probability, in many of the cases that have been recorded as cures following operations for tumor of the bladder, these tumors have been gummata, and neither malignant nor simple papillomata. These syphilitic lesions have more of a tendency to grow upward and less of a tendency to infiltrate the bladder wall than malignant growths. From either malignant growths or from benign papillomata they are at times extremely difficult to differentiate, and when possible a careful microscopical examination of any bladder growths should be made. Probably where a syphilitic ulceration of the bladder has been marked, its after-effect is to cause connective tissue in the bladder wall and give rise to contracted bladder. It may also be stated that many cases of late syphilis of the nervous system, such as locomotor ataxia, have syphilis of the bladder as well, instead of having their bladder symptoms entirely due to some

sclerotic or other condition in the spinal cord; syphilis of the bladder may coexist with them. In these cases mild anti-syphilitic treatment is of benefit for the bladder symptoms, in addition to whatever local treatment may be given them. In all doubtful cases of bladder lesion portrayed by the cystoscope, all other diagnostic factors possible to obtain should be collected and analyzed before a diagnosis of the presence or absence of malignant growth of the bladder is made.

CHAPTER VI

General Consideration of the Condition of Blood, Hair, Nails, and Saliva

In addition to what has previously been mentioned in this volume concerning the various methods to be considered in the diagnosis of malignant growths, there are a few others which we believe will, in the not far-distant future, be taken into account as diagnostic factors, and concerning which at the present time comparatively little is known or has been written. They are of enough importance at least to be mentioned.

Concerning the *blood* in general, as regards its chemical analysis, there is still a great deal of work to be done to establish definitely the amount of the chemical constituents in normal blood, and also in the discovery of new tests which will demonstrate the amount present of some of its constituents, where only small quantities of blood can be obtained for examination.

The work done by us apparently demon-

strates what the normal amount of sulphur is in the blood, about 36 milligrams to 100 c.c. of blood. But still further work needs to be done to demonstrate the absolute correctness of these figures, that is, as to whether this increase of sulphur in the blood is found in carcinoma alone or not, as our work would seem to show, and further work in the chemistry of the blood is needed to demonstrate the normal amount of potash and some other substances. It would appear that, within the next few years, judging from the rapid advance made recently in discovering new methods for estimating the chemical constituents of the blood, the chemist will be more and more frequently called on to examine the chemical blood constituents in given cases. It would also appear that these examinations will be made with increasing ease and be of more and more frequent aid in the diagnosis of many diseased conditions. In addition to the information that can be obtained from the blood at the present time, and what may be expected from its chemical analysis in the near future, there are other factors, such as the observation of the hair, condition of the nails, and chemical examination of the saliva, which may render at times valuable information.

We are indebted to the observations of an ardent believer and scientific worker on the subject of sulphur changes in the urine and sulphur metabolism in the system in cancer generally, Dr. F. von Oefele, for the observation that "*Bald-headed men never have cancer*" ("Quantitative Urine Analysis, with Special Reference to Carcinoma Metabolism," *Trans. Ger. Med. Soc.*, March 4, 1912). Naturally this statement can only be taken semi-seriously, for the loss of hair from the scalp can be due to many different causes. But in a general way there is probably some truth in the statement, for it seems to be true that sulphur plays a very important part in the development of the hair, and that the lack of sulphur also plays a part in causing its loss. Sulphur changes are, possibly, the cause of the falling out of the hair after an acute infectious disease like typhoid. Sulphur which would naturally tend to nourish the hair and the scalp is used up in the intestinal canal in overcoming the products of decomposition caused by the activity of the infected condition appearing there. With the increase of sulphur in the system, such as appears to exist in individuals with malignant growths, it might be expected that the hair would re-

ceive its proper amount of nourishment as far as sulphur is concerned; and, the other factors being normal, bald-headed people would be less subject to malignant growths, so far as the lack of hair is an indication of a lack of an increase of sulphur in the system.

The condition of the *nails* may not, and probably do not, demonstrate anything of diagnostic value of a malignant growth. The probabilities are that the sulphur element in the development of the nails is comparatively a minor factor. Split nails may show a lack of potash, which is supposed to be increased in the case in most individuals suffering from malignant disease, and in that way be an indication that no such diseased condition exists. So far as our own observations go, it is so limited in this respect as to have but little value. It is only mentioned, however, as one of the factors that should be borne in mind, observed, and recorded in history taking.

The *saliva*, concerning the chemical analysis of which comparatively little work has ever been done, may, through its examination, occasionally furnish valuable data. Sulphur exists in it in the form of sulphur cyanate. When the normal amount is finally ascertained and some easy test devised to determine the excess

or diminution, it may furnish an easy method not only of aiding in the diagnosis as to whether or not some departure from ordinary tissue metamorphosis exists, but also be a guide in showing the effects on such metamorphosis of any remedial measures which may be undertaken.

These examinations should be of important value in connection with such conditions as "Smoker's Patch," the origin of which is sometimes very difficult to determine.

PART IV

TREATMENT OF CANCER

CHAPTER I

Basis of All Successful Treatment to be Found in Measures Which Tend to Increase Tissue Metamorphosis

Success in the treatment of cancer, like that of many other diseases, will depend to a great extent on the diagnosis; on the correctness of this, and the recognition of cancer in its earlier stage, the principles of treatment are founded. It is more than possible, it is probable, that through the recognition of a precancerous state, if such a term can justifiably be used, the adoption of proper methods, both hygienic and medicinal, to increase tissue metamorphosis, will often prevent the disease from becoming constitutional, prolong the life of the individual, diminish suffering, and what may be of even greater importance, limit the activity of the predilection to the disease

which may be transmitted to others. Individuals in whose family history may be traced a predilection for cancer, in whom the neutral sulphur constituent of the blood and the urine are found to be above the normal, who show a tendency towards a slow repair following injury or accident, and particularly those whose mucous membranes are unusually easily subject to excoration, or such conditions as relapsing herpes from slight irritation, belong to this class.

The above conditions, or similar ones, are considered of sufficient importance to be referred to more than once in other portions of this book. Concerning the medicinal treatment in general to be adopted, it is difficult to separate the preparations to be used into clearly defined classes. Somewhat generally speaking, it may be stated that for internal administration one class consists of preparations which can probably be considered as tonics. And even the action of these is not at the present time clearly and distinctly understood, but they probably act on the hematin in the blood, and through increasing the hematin in the blood increase the resistant power in the cell. To this class belong arsenic, iron, manganese, and vanadium. An-

other class of agents, such as selenium and tellurium, act as diuretics, as oxidizers, or else in some way with which we are not entirely familiar, enter into combination with the sulphur in the cell in such a form as to tend to stop increased cancer-cell proliferation. If they act as oxidizers, it might be surmised that the neutral sulphur would be changed to sulphates, and that an increase in the latter and a diminution of the former would be found to follow their administration.

The third class contains such constituents as condurango, echinacea and the like, whose action has so far been undetermined, but in advising the use of which our experience corroborates that of some others as to the beneficial results following their administration, which is at the present time (at least to a considerable extent) empirical.

The above refers to preparations for internal administration. To a considerable extent the same preparations not infrequently in a different chemical combination will be found to be useful for external application for ulcerations associated with malignant growths, but which are not malignant growths themselves. Reference is here made to the state-

ment in one of the earlier chapters that the ulceration is not the disease, but is merely one of its manifestations, and it is also necessary to keep the surrounding tissue in as aseptic a state as possible, so as to prevent further infection. This is in addition to whatever direct application over ulcerated surfaces may be made of a stimulating nature, such as radium, X-ray, arsenous acid paste, or any other cauterizing agencies; applications to certain ulcerations are also necessary to prevent the odor or to relieve pain. It has been found by us, that for an external application that will relieve the odor, where skin surfaces are ulcerated, tend to stop the spread of the ulceration and relieve the pain, a modification of Dakin's solution is the most useful, made according to our formula given later on, to which has been added a slight amount of selenium or tellurium. This, we consider, is the most useful, although the absolutely ideal preparations for this purpose have not as yet been found, and probably never will be, as there are too many different opposing factors to be controlled to make any one preparation fulfil all the indications. Ointments which contain vanadium and selenium in an unirritating base are sometimes

useful either in protecting surfaces adjacent to the ulcerated area, or through their effect as an inunction in administering selenium to the system. There are several preparations on the market for this purpose, but care should be observed when using them not to let them touch the ulcerated surfaces directly, as they cause irritation. Concerning deodorizers, the difficulty met with in solutions as deodorizers is, that a true deodorizer is a difficult thing to discover. Chlorine in some form which acts as a disguiser of any unpleasant odor is good, but is in almost all forms apt to be irritating. The preparation which we present further on, with a definite statement as to its manufacture, is the least irritating and the most useful that we have so far been able to obtain. Our experience with some of the preparations for external use that will relieve pain, such as orthoform, although recommended by many, has been disappointing. Aristol, lead and opium wash, and many unirritating ointments, all have their place according to the needed requirements of the individuals.

We prefer to mention throughout this work the substances which we ourselves have found to be the most beneficial. And at the

risk of repetition it may be stated that the Dakin's solution made according to the method which we give, and with the addition which we recommend, is not only of great aid from its constituents, but from the method of applying it through the tubes, a constantly moist application to the ulcerated surfaces is insured.

Life in the open air for these poor sufferers is very beneficial. In this part of the world they are always better in summer than in winter. It has never been thoroughly tried out so far as we are aware, but it would not be surprising if in days to come it was found that life in the open air would be of almost as much benefit to individuals suffering from cancer where the diagnosis has been made of its existence in the earlier stages, as previously referred to, as it is in cases of tuberculosis. One of us was exceedingly surprised and pleased to observe in a visit made to the home for incurables at Hawthorne, N. Y., some few months ago, the wonderful vitality exhibited by the patients in this home for incurable cancer. Several patients there with cancer of the stomach had been inmates from several months to several years, in whom, while the diseased condition was not cured, it had ap-

parently been arrested. In that institution, outside of the comfortable hygienic surroundings, good nursing, and abundant food supply, the improvement could only be attributed to the abundance of fresh country air, the institution being situated on a hill a few hundred feet above the sea level.

The probabilities are that these cases do better under the same climatic conditions as tuberculosis patients do. But so far as we are aware, statistics are lacking to show the best climatic conditions for these people. The same rules should probably apply as are found the best in sanitariums for sufferers from tuberculosis. They should keep in the open air practically all the time, with an abundant food supply, and be provided with some occupation so far as the given case permits. If such conditions as frequent retardation of the malignant growth exists, as we found in the institution mentioned above, which is considered a home for incurables, and in which, so far as we are able to observe, no medicinal treatment beyond ordinary palliative measures was administered, what might not be hoped for in similar institutions if the diagnosis was made early, and a systematic method of medicinal treatment, in addition, carried

out? Unfortunately, the death rate in homes for incurable cancer in the large cities is extremely high. The main reason for this is that patients are received there practically moribund, and in such a state that their system has been thoroughly undermined by a general carcinomatosis, with not only one but so many infected processes at work that ordinarily anything beyond the relief of pain is practically impossible. Even in such institutions, however, more attention to details in the carrying out of some properly formulated and well-planned remedial measures will lower the death rate, and very materially increase the number of patients who could be discharged if not cured, at any rate with the diseased condition practically arrested. At present this rarely happens.

The food supply is one concerning which there has been considerable discussion; dietary sheets have been compiled according to the point of view concerning the cause of cancer which is held by the attendant. It is hardly our desire to go into a discussion of the various regimens which have been suggested. Up to the present time we are of the opinion that under ordinary circumstances a mixed diet of well-cooked food is preferable, modi-

fied necessarily according to circumstances surrounding any given case. It has been suggested by some, very cleverly and perhaps wisely, that an attempt should be made to use food as free as possible from sulphur. An interesting article has been written by Dr. Kessler concerning this sulphur-free diet ("Diet in Carcinoma," *N. Y. Med. Jour.,* 1912). If our view of the sulphur metabolism is the correct one, the condition of the individual will neither be improved nor made worse by withholding the ordinary amount of sulphur constituents from the system.

It is hardly necessary to speak about bathing, more than to say that it is an advantage in keeping the skin in as good a condition as possible, and above all of value as the circumstances surrounding any given case will permit of inducing perspiration as a method of cleaning the inside of the skin, relieving the kidneys, and improving the general condition. In fact, some medicinal preparations used for malignant growth have probably been of benefit through their action in stimulating perspiration.

CHAPTER II

Vanadium and Arsenic. Iron and Manganese. Condurango, and Other Bitter Tonics

Having found (as stated in previous chapters) that all oxidizing agents properly applied are of benefit in cancer, we state, as simply as possible, the manner of using the above-mentioned remedies which we have found most useful, believing that in so doing we avoid going beyond the limitations of this work and invading the field of polypharmacy.

It is claimed that vanadium is more powerful than arsenic, while its toxic effects are about one-tenth less. Solutions of soluble salts in strengths of from 1-20,000 to 1-50,000 make very good antiseptics. Our experience with vanadium is limited, but sufficient to make us consider it worthy of further investigation; it may prove to be a much better tonic than arsenic. It can also be combined

with selenium, to make salts of the two elements, Vanadium selenides, of which there may be several, di-, tri-, tetra-, penta-selenides, V_2Se_2, V_2Se_3, V_2Se_4, V_2Se_5. These combinations are very insoluble, and therefore for internal use they are unsatisfactory. When, however, any of these vanadium selenides are combined with either potassium or sodium they form potassium selenovanadate, or sodium selenovanadate, both of which are soluble.

Solutions of these have been given in doses of from one to two milligrams three times daily, and it is reported that satisfactory results have been obtained from their use.

For external use, preparations of vanadium and selenium, the vanadium tri- or penta-selenide, in the form of 3 per cent to 5 per cent ointment, have proven satisfactory. The base recommended is a combination of eucerine and lanoline.

Within the last few years several preparations of vanadium by different manufacturers either in this country or abroad have appeared. So far they have been used to a very limited extent. Within the last four or five years they have received some recognition either alone or combined with other elements,

as a method of retarding growths. Their use has been recommended for internal administration or for external application for the same purpose either alone or combined with selenium, or with an ointment base as mentioned above. When used combined with selenium externally it has been with the idea of administering selenium through inunction for its constitutional effects, and with the idea of making the action of the former less depressing. The exact action of vanadium has not yet been studied carefully enough to be understood, but it probably has a constitutional effect resembling that of arsenic more closely than any other element; acting as a tonic and as an antiseptic in some way, toning up the cell by the above measures and making the tissues become more resistant to bacterial invasion. It is never administered in a metallic state internally, but always as a soluble salt, and generally in combination with some other element or acid radical. When administered alone it is generally given in the form of vanadic acid or vanadium oxychloride solution. We have not had any experience with this element administered alone, but we have observed its effects in several cases when given in one to two milligram doses three times a

day, when administered as potassium seleno-vanadate. This solution is probably one which is somewhat unstable, and not as easy to obtain as colloidal selenium, but in the few cases in which we have tried it the results have apparently been as satisfactory as could be expected, and no depressing after-effects have been noticed to follow its administration.

Vanadium oxychloride, vanadium sulphate, or any soluble salt has been used for antiseptic solution in the strength of 1-20,000 to 1-50,000.

Arsenic, since its discovery, has justified its reputation as a useful remedy for diseases of the skin, and also as an alternative oxidizing tonic for the system when administered internally, and probably in some form or other, either externally, internally, hypodermically, or intravenously, is employed more than any other strictly medicinal agent for cancer. In our experience with it, which, while somewhat limited, has been to a great extent in far advanced cases, we have not found it as useful as the proper preparation of selenium, vanadium, and to some extent tellurium. But aside from these it seems about as useful as, and safer than, some of the other more re-

cently discovered methods for the treatment of this disease.

It should be noted that as an oxidizing agent arsenic and vanadium are concerned principally with carbon, and hydrogen, while oxygen is the compound with which selenium and tellurium are most intimately associated.

Again, at the risk of indulging in repetition, we wish to call attention to the fact that there is a wonderful resemblance in cases of old syphilis and of cancer; in some form they seem to be cousins, and while arsenic gives very brilliant results when administered internally, or especially intravenously in the form of salvarsan, very great care indeed should be used to be sure that a proper differentiation has been made between these two diseases. Arsenic in the form of salvarsan, neosalvarsan, or some of its substitutes, should, when practicable, be administered in two large doses at intervals of a week, and its effect watched in all doubtful cases, and in those in which the slightest uncertainty exists, even if a month's previous treatment by means of mercury and the iodides has caused no effect. Salvarsan and neosalvarsan have been used as remedies for undoubted carcin-

oma itself, with apparently occasional benefit, and recently they have been recommended by such an exhaustive writer on the subject as Roncali (Trattato di Neoplasmi Maligni, Torino, 1916). He finds its administration more efficacious in the connective-tissue than in the epithelium growth.

In the administration of arsenic internally as an oxidizing tonic, ordinarily we prescribe a fifth of a grain of arsenous acid in the form of a freshly made pill dusted over with black pepper, three or more times a day; this is the "Pil. Asiatica" of the old pharmacopœias. We have not infrequently found arsenous acid paste of great value as an external application to epithelioma of the skin, naturally not the mucous membranes; we have sometimes found this apparently of more benefit than excision, particularly in places like the angle of the eye, where excision was a difficult and awkward operation to perform, and it has also been of great use in cases of epithelioma after the application of radium and the X-ray had proved inefficient. We use the paste, of which the following is the formula:

Arsenic Paste

Acid arsenous, one-half dram.
Amylum,
Powdered alum, } of each, two drams
Glycerine,
Distilled water, one-half dram.
Mix.

This is approximately 7 per cent; we also use it in a strength of 10 per cent and 15 per cent. If this paste becomes too hard for application it should be warmed, before using, in a warm bath; a little hot water may also be added. It is sometimes difficult to tell which strength is the best adapted for the individual until two or three have been tried out. The application should be of a strength sufficient to cause reaction, such as swelling, reddening, and possibly some increase in discharge, for from one to two weeks after its application, during which time some simple ointment like cold cream should be applied, and when the reaction has entirely subsided another application should be made of the same strength or stronger, as is held to be the correct view for the particular case. This paste should simply be painted over the surface of the ulcerated area, not beyond it,

lightly but thoroughly, with a cotton or wooden applicator, once. The reaction will start immediately. But again attention must be called to the fact that where the external applications of arsenous acid paste seem to be of great benefit it is well to combine with them the internal administration of selenium and vanadium or some other of the oxidizing elements of like nature already mentioned. Where it is not practicable to obtain these in their proper form arsenic should also be administered internally as well as externally, and with the proper periods of rest, so as to avoid its cumulative effects during the remaining lifetime of the patient.

Iron, the well-known oxidizer when administered in such form as not to irritate, is of great value in cases of carcinoma, in association with whatever other methods may be tried, except possibly some of the newer oxidizing agents mentioned, which apparently do better when administered by themselves. Naturally enough, in cases far advanced, it has been noted by others (and written about) that a profound anemia is apt to exist with a marked carcinomatosis; in this condition, with the exception mentioned above, like other oxidizing substances, iron is indicated,

in addition to that even where the blood-count or hemoglobin are not materially reduced. It is well to use it in whatever form is found to be the least irritating; as, tartrate of iron and potassium, or as a peptonate, or it can be combined with manganese, which deservedly enjoys a reputation as an oxidizing agent. This may be administered with iron, or separately, often, and in as large a dose as can be borne without causing irritation, and for long periods of time. The idea being that all of the above, together with the proper hygienic surroundings, excision, radium, X-ray, or other agents, may help to retard the growth of the cancer, even if it is not cured; so that the individual may live in comparative ease, and possibly die of some intercurrent disease which is apt to cause less suffering than cancer.

We now come to consider a class of remedies concerning the therapeutic effects of which but little is known; but as a result of our observations we believe that some of them are of service; but in what way they are a benefit is a problem for the physiological chemist to work out. Since the beginning of time, apparently, herbs of various kinds have enjoyed a reputation for their beneficial ef-

fects on cancer. This has been particularly true among natives in inaccessible regions, where medical aid has been hard to obtain. It is interesting to note that they often have a remedy for snake-bite and for cancer. Generally, they are found to be preparations which induce perspiration. Dried violet flowers, in our observation, seems to have been the favorite in this respect; made into a tea and drunk freely, it certainly seems a useful remedy to induce perspiration, and has been recommended by some scientific workers as useful for certain forms of skin disease. The tea made from hemlock buds, also, has its reputation, but in this the amount of resin is considerable, and is liable to cause gastric irritation. There are some two or three bitter tonics which we have used that have apparently been of benefit, whether by increasing tissue metamorphosis in such a way as to help oxidize the amount of neutral sulphur apparently always present, or whether simply by stimulating the digestive organs so that they aid in assimilation of food, is beyond our knowledge. Of these, condurango occupies the first place; echinacea administered with it may or may not add to its value. We have, therefore, been in the habit of administering

to those cancer patients, where we have not been able to obtain the other oxidizers which we have found to occupy the first rank (as selenium and vanadium), the bitter tonic of which the following is the formula:

Bitter Tonic

Condurango bark,
Sarsaparilla root,
Columbo root,
Echinacea,
} of each, half ounce

Boiling water, enough to make one pint.
Make infusion, and filter.
Dose: Half ounce in water half hour before meals.

We have found it to be well borne and of apparent benefit, even by those suffering from profound general carcinomatosis; although, of course, it is not recommended in any way as a cure-all. For the skilful preparation of this, as well as the arsenous acid paste recommended above, we are indebted to the kind offices of our friend, Mr. Louis Protzmann, a well-known pharmaceutical chemist of this city.

CHAPTER III

RADIUM, X-RAY

The more the investigator carefully examines the evidence furnished by the later methods of the treatment of malignant growths, and separates out as far as possible from such evidence the mass of conflicting testimony, both *pro* and *con*, which must be thrown aside from the unreliability of its source (this term being used to cover irregularities in reports due to varying causes), the more forcibly is the investigator confirmed in any views held as to the constitutional character of carcinoma, and the more profound is the conviction that the varying lesions treated are, and can only be, local manifestations from constitutional disturbance. Among the later and most carefully worked out are the treatments of such lesions by radium and the X-ray. In the fourth edition of the work of Greene and Brooks, 1917, previously referred to, the statement is made that radium has come to stay. Since its publication further experience

and consideration of cases previously treated has not made it necessary to attempt to modify that statement. But like many other procedures, both surgical and medical, which have been heralded with considerable enthusiasm, too much has been claimed for radium on the one hand, and on the other hand scepticism has been too pronounced. Attention is called to a conscientious and scientific work recently published, "Radium Therapy and Cancer," by Henry H. Janeway, M.D., Benjamin S. Barringer, M.D., and Ghoacchino Failla, E.E., A.M., published by Paul B. Hoeber, New York, 1917. Particularly to be read are the general conclusions of Dr. Janeway, page 222. Our conclusions concerning the value of the use of this element up to the present time are as follows: that radium, like other factors that can be employed, will not cure cancer. It will sometimes cure lesions caused by cancer, and by so doing retard cancer better than any other agent that can be used. Its use seems to be of particular benefit in cancer of the mucous membranes. Our own experience in the use of this substance, either when demonstrated in our own cases or in cases which have come under our observation, has not been extensive. On the other hand,

it has been interesting, and has covered fairly well quite a few lesions due to cancer of various types, and also such a sufficient period of time that that valuable factor has helped us in the formation of our conclusions.

Very little, purposely, has been recorded in this volume regarding individual cases; but just here space will be occupied in mentioning a few cases which demonstrate the characteristic effects of radium. Two of the younger men associated with us at the time were the first in this country, so far as we are aware, to try radium for carcinoma of the bladder. A few months after the radium had been applied, the application in each case having been made through a supra-pubic incision, the cases were reported at the New York Academy of Medicine and published ("Application of Radium in the Bladder for Carcinoma, with Report of Two Cases," F. J. Schoenenberger, M.D., and William Schapira, M.D., *The Journal of the American Medical Association*). One of these patients died, apparently from metastasis in the kidney, about six months after the application of the radium, the bladder in the meantime having been apparently cured. The bladder lesion in the second case was also apparently

cured, the man gained many pounds in weight, cystoscopic examination failed to show anything but a scar where the growth had been, and in this case part of the growth had been removed by excision for microscopical examination. He continued in this condition for two years, at the end of which time he was lost sight of. At the end of three years he appeared in the wards of the hospital with which one of us is connected, with an extensive reappearance of the cancer of the bladder, at the seat of the previous lesion, and died under our observation within a few weeks. Another interesting case was that of a woman who came under our care, for a small papillomatous growth, appearing six months after an operation for the removal of the uterus and ovaries, through the vagina. The diagnosis was confirmed by microscopical examination. When a papilloma appeared in the vagina at the apex of the old scar the case was referred from the hospital in which she had been operated on to a home for incurables, and on account of the hemorrhage was referred to one of us. Cauterization had no effect on this growth. The patient was very thin and weak; hemoglobin 50 per cent, Wassermann negative, cachectic

appearance. Finding other measures give no relief, two applications of radium emanations were made. About two weeks after the first one the growth, which was about the size of the end of the little finger, disappeared. The hemorrhages ceased, the woman lived a year, and then died, apparently from a general carcinomatosis. It was impossible to obtain an autopsy. In this case it seems undoubted, as in the one recorded above, that the use of radium prolonged life.

At the present time cancer therapy by means of radium is so associated with its treatment by X-ray that the two should probably be considered together. To a considerable extent the nature of the treatment is the same, and it is also true that a persistent search is being made with both of these methods to find out more about the laws under which they work, the right dosage of both for any given case, and the safeguards to be employed in their use.

Radium can be made to penetrate the tissues deeper than the X-ray, and naturally is much more expensive to use, and more difficult to obtain. Following operations for such conditions as carcinoma of the breast, one or two applications of radium may be made, fol-

lowed later on by a more diffuse and general application of the X-ray over the mediastinum and adjacent parts. In other words, the X-ray is apparently being used more diffusely now than was the former custom when X-ray applications were first applied.

Attention is being called to the very ingenious methods of Dr. Murphy, of the Rockefeller Institute, concerning which comparatively little has been written ("Heteroplastic Tissue Grafting through Roentgen-Ray Lymphoid Destruction," *The Journal of the American Medical Association,* 1917). His method, as we understand it, consists in the application of comparatively mild doses of the X-ray upon such conditions as carcinoma recurring in old scars following excision, the strength and frequency of the application being regulated by its effect upon the lymphatics. The idea being that in mild doses its application may encourage lymphocytosis, and through that means have an inhibitory effect upon the growth; whereas, if the strength of the application was too severe it would be shown by the destruction of these elements, and through this measure increase the activity of the malignant processes. It can be safely stated that so far the beneficial ac-

tion of the X-ray in its various forms seems to be confined almost entirely to smaller lesions, particularly those upon the skin, and that its use apparently has never been demonstrated to be of any great value for the deeper-seated lesions, like those in the mediastinal glands; but experiments in this latter direction are being made, as mentioned above.

If our conception of malignant growths is correct, as we believe it is, to the extent that we have expressed it, that carcinoma is a constitutional disease, it would not be expected, then, that X-ray therapy would have any greatly beneficial effect upon it, more than to be of considerable aid in certain of its skin manifestations. Under such limitations it would seem to us as if the method suggested by Dr. Murphy is a valuable one, and that in certain cases beneficial results might be expected to follow its administration in the manner suggested by him. Fulguration also has, we believe, a useful field (but one not yet clearly defined) in the removal of small growths either on the skin or mucous membranes.

CHAPTER IV

Excision

The value of excision as a therapeutic measure in various forms of cancer is a somewhat difficult one to write about, as so many perplexing questions necessarily arise in connection with it. Among others, is the proper amount of consideration to be given to various divergent views. The road is a long one between the views of those who believe that "cancer can be cured without a knife" and those who advocate the removal of large areas of tissue and all lymphatic glands possible to be found in the vicinity of the growth, and even go so far as to recommend such procedures as female castration for carcinoma of the breast.

It will be easier for those who have read the preceding chapters to understand our views, which are founded not only on our own belief in the nature of the processes to be dwelt with, previously recorded, but also on the results of our clinical observations and

experience in surgical procedures; and while to some degree they may diverge from the extreme views held by many, they also to a considerable extent tend to bring many of the divergent views into a certain amount of accord.

We realize that, in making the statement that the value of excision for a growth as a therapeutic measure will depend upon the circumstances surrounding each given case, we offer nothing new. But the refinements of diagnosis now at the command of the surgeon, to which we have endeavored to make some contribution on our part, enable him to understand the circumstances which surround any individual case much more clearly than would have been possible a few years ago. We make the statement clearly that, in our belief, "no operation will cure cancer." On the other hand, a statement can be made with equal truth that the proper operative procedures will often retard its active development to such an extent that the individual's life can be prolonged for many years, so that they may die from some intercurrent disease, and that they are often our best therapeutic procedure.

Whatever may be its finer, primary, patho-

logical, or original cause—that cancer (like syphilis or tuberculosis) is a constitutional disease, there seems to us no doubt; and operations for the cure of cancer no more cure cancer, however much they may retard it, than does the removal of a tuberculous kidney cure tuberculosis; although both may be of help to the individual. Possibly the removal of a gumma might, and probably often has, when it has been removed through a mistake in diagnosis, aided in the same way a syphilitic individual.

The factors to be considered in determining the character of the operation to be performed are: (1) heredity; (2) nature of the growth; (3) extent of the growth, particularly as determined by carefully taken skiographic pictures; (4) previous treatment; and (5) the general condition of the patient.

A consideration of the above should tend to modify the decision as to the operation and its character.

The above refers to operative procedures for primary and generally extensive lesions of cancer, when of more than a palliative character. The indications for these latter are often present, and naturally they frequently are, and should be undertaken for the

purpose, if not of prolonging life to any great extent, for the relief of hemorrhage, pain, and general discomfort. In connection with operations, and basing our opinions not only on the results of our own, but that observed from the surgical work of others, we believe that the mistake more often made than any other is the neglect of the after constitutional treatment of patients, following whatever operative procedure may have been instituted, whether with the hope of a radical cure or as a palliative measure. The details of such treatment are recorded in other chapters of this work. This neglect is evidently based on a very general misconception (which however, is, we believe, being gradually overcome) of the nature of the disease.

That the above statement is correct will be forcibly impressed upon those observers who have been given the opportunity to carefully examine cases which come to institutions that are intended for the treatment of malignant growths; and, above all, those who have observed condition of affairs as they exist in the various homes for incurables. Even in these latter, there is a tendency to too much laxity in careful history taking and supervision of both hygienic and medicinal remedial meas-

ures. Not infrequently in them are the proper measures for diagnosis overlooked, and carelessness used in the methods to differentiate malignant growths from the later lesions of syphilis, which could be easily benefited by constitutional measures. In such institutions suffering should be ameliorated by the proper application of every suitable remedy, both external and internal. In addition to the above, by proper laboratory, out-patient, and autopsical work, some of these places which are now used mainly as homes for the unfortunate to die in would become, in addition, centers for scientific research, and thus aid in the discovery of new methods for the combating of disease.

In closing this chapter we wish again to emphasize the fact that in any given case, before operating, the surgeon should be sure that he has used, if not all, at least all practicable diagnostic procedures that are at hand, among the most important of which may be again mentioned the necessity of a stereoscopic X-ray picture, and, when possible, examination of the sulphur contents of the blood and urine.

CHAPTER V

Selenium and Tellurium

Mendeleeff has divided all the elements into groups according to their atomic weights and properties. According to this classification it appears that the properties of the elements bear the same relation to one another as that manifested by the atomic weights. According to this grouping, selenium is placed in the same group with sulphur, which means that its properties, chemical and physical, are analogous to that of sulphur. In addition to the chemical and physical properties of these elements, we find that their biochemical properties depend as well upon the grouping of Mendeleeff. In its physical forms selenium closely resembles sulphur; that is, it may assume several allotropic forms, but, however, it differs from sulphur in the fact that it is a metal. Like sulphur, it forms binary compounds, analogous to the sulphides. These compounds are called selenides. In its metallic form it forms salts, and one of the

most interesting compounds of this type is the sulpho-cyanate. The compound of selenium that oxidizes possesses colloidal properties and is generally referred to as colloidal selenium.

The fact that selenium and sulphur belong to the same group means that selenium has the property of replacing sulphur compounds, and this fact is of extreme importance in its biological relations. Only a limited amount of work has been done upon the biochemical properties of selenium and selenium salts. They are chiefly stated as follows: If selenous salts are administered, they are excreted in the urine as such. On the contrary, if selenic salts are given, the selenium is excreted in the form of selenous compounds; this means that selenic salts have been deprived of their oxygen, and this oxygen has been utilized in oxidation processes within the body. Further, it has been observed that this oxidation by the selenic salts is confined principally to sulphur compounds. On the other hand, arsenic and vanadium in their compounds may act as oxidizing agents, but their oxidation is concerned principally with carbon and hydrogen.

Another interesting fact concerning the effect of selenium salts upon the organism has

been demonstrated by Wassermann. He observed that the administration of selenium salts led to an increased output of uric acid, urea, and creatinine. In confirmation of these investigations we must state that our results, obtained from the blood of a patient receiving the selenium compound, has shown that the concentration of uric acid in the blood was far below normal, that is, less than .5 of a milligram to 100 c.c., and likewise the amount of urea and creatinine in the blood was abnormally low. This means that the kidneys were stimulated to increased activity. Selenium compounds likewise produce a phagocytosis, a fact of great importance therapeutically where we are dealing with an infection superimposed upon a carcinomatous condition.

The most important problem presented to the chemist in the therapeutic application of selenium compounds is the elaboration of a product of selenium which is soluble, easily assimilated, and non-poisonous. Selenium itself is not soluble, and therefore is of little value. All the salts employed by Wassermann were, on continued application, toxic. But later investigations have shown that it is possible to produce compounds with no

toxic properties. The most commonly employed compounds are potassium seleno-cyanate. This compound is analogous to the sulpho-cyanate of potassium. However, the selenium is taking the place of the sulphur. We do not recommend the use of the seleno-cyanates, except with extraordinary caution, inasmuch as they contain the CN group, and they have been observed to have a cardiac depressant effect. If we wish to effect a complete oxidation, and therefore an excretion in an innocuous form of the product which we have observed in the blood, the increased sulphur and non-protein content, the most logical therapeutic agent to apply is the compound of selenium and vanadium with potassium, commonly known as potassium seleno-vanadate. In this compound the oxidation of the sulphur and nitrogen is effected by the selenium, while the oxidation of the carbon and hydrogen is brought about by the vanadium. In addition to the fact that the selenium has the effect of a diuretic, and although little is known concerning the potash metabolism in carcinomatous conditions, from the results obtained it is safe to say that the administration of potash salts is apt to be followed by an improvement in the condition.

While the administration of the above preparation has been attended with good results, when administered in the form of a solution, probably for ordinary commercial purposes, it is not as practical, and its therapeutic properties will not be preserved for as long a period as if it is administered in the form of a tablet, of colloidal selenium, with the action of which we are also familiar. It may be used in administration by mouth, by injection intravenously, and intramuscularly. Our results lead us to recommend the oral administration. During the intake of selenium salts the sulphur excretion of the patient must be carefully observed. It will be noted that an increased output of the sulphates with a corresponding decrease of the neutral sulphur closely follows the administration of selenium. The point will be reached where the intake of selenium has become so great that it is no longer fixed in the tissues or utilized in oxidation. It may then be detected in the urine in the form of the hydrogen compound. Hydrogen selenide has a very disagreeable penetrating odor, suggestive of decayed horseradish, and its presence in the urine may be readily detected in this manner. At the same time the patient

will complain of a continuous bad taste in the mouth. At this point the selenium administration should be discontinued until the selenium is no longer excreted, and then the selenium compound may be given a second time in small doses and at longer intervals. Histo-chemical studies have shown that selenium is assimilated by the tissue cells, and principally by the cells of a malignant neoplasm. Following this fixation of selenium a diminution in the size of the neoplasm and of the malignant character of its cells may be noted. Furthermore, a fact of extreme importance in dealing with advanced cancers is that selenium administration is characterized by a decrease in the intensity of pain. During the administration of selenium we have found it wise to gradually diminish the amount of morphine taken by the patient, because the intake of morphine is a disturbing factor, and, in fact, after a time the administration of morphine may become unnecessary.

In dealing with malignancies of the bladder, hematuria is either a constant or intermittent factor. The administration of selenium often decreases this hematuria. Most probably this is due to an astringent action of the compound.

We have observed the effects of selenium on inoperable cases, and also following operation in cases of extensive malignancy, as well as in cases of comparatively mild cancerous invasion, such as a small epithelioma of the skin; and we believe that it has properties which, if thoroughly understood and studied, will result in its administration universally and extensively to prevent the occurrence of pain in pre-cancerous cases, and to relieve the pain and retard the growth of those cases which are further advanced. It has been supposed to render certain inoperable cases operable, but so far such cases have not come under our direct observation.

We have used several different preparations of selenium. Some of them have a depressing effect upon the heart, as has been previously mentioned, and the various cyanides of selenium should not be administered internally on account of the latter effect. Selenium may be used in the form of an inunction, in an ointment base, to obtain its constitutional effects; if so desired it can be used for that purpose, as there are at the present time on the market some preparations of selenium with an easily absorbable ointment base, combined with vanadium. This is, however, a somewhat

uncertain method of administration and it is locally irritating when it comes in contact with an ulcerated surface. As a result of our investigations we recommend the internal administration of colloidal selenium. Colloidal selenium has been furnished us in the form of a tablet combined with a physiological salt, in which it is stated that the sodium of the salt has been replaced by potassium; there is one and one-half milligram of colloidal selenium in each tablet. We believe the potassium salts are the best for this purpose. These tablets give no depressing after-effects. They should be administered in somewhat the same manner that mercury is given for syphilis. Ordinarily the dose should be increased until the toxic effects of the selenium are apparent; two tablets after meals, three times a day for one week in the beginning, then one tablet three times daily for one week until the system becomes saturated with selenium. By this we mean that the degree of oxidation will be continuous, theoretically, as shown by its effects in reducing the amount of neutral sulphur in the urine, which should be observed weekly for this purpose. Any toxic effects of selenium generally show themselves by a garlicky odor to the breath and the pa-

tient will complain that everything has a characteristic taste of the odor mentioned. If its use is pushed further, general depressing effects may be observed on the system, together with an increased amount of pain, which will previously have been noticed to diminish or disappear, and an increased amount of neutral sulphur will make its appearance in the urine. Our experience, so far, has not always borne out just the results which might be anticipated, as mentioned above; enough sulphur examinations associated with selenium have not been made by us to enable us to make a positive statement as to its effect in that respect, but in certain cases in which we have made these examinations the above contention has been borne out. In all cases in which we have administered selenium, irrespective of the preparation of selenium which has been given, there has been a diminution of pain following its administration so marked as to lead us to believe that it does have a direct action in that respect. Also, while we have seen such toxic effects as a garlicky taste follow the prolonged administration of the colloidal selenium, we have never seen any bad after-effects, while we have seen gratifying results so marked as to make us believe

that it does have, in certain cases at least, a marked constitutional effect for the better. At the same time we have no desire to recommend it as a cure-all, but within the lines following the laws under which its effects appear, benefit will undoubtedly follow its administration.

We have used it previous to operation, in a far advanced case that refused operation, without any apparent result; but its continuous use following operation, consent having been given later, in the same case, which showed a tendency to malignancy to occur in the old scar, has been attended with good results, apparently a complete recovery taking place.

In another case following operation and radium for malignant growth in an extensive area, recurrence has taken place, its use has apparently in some way arrested such progress and restored the individual to a comparatively healthful state.

In a far advanced case, such as reinvasion following the operation for the removal of both breasts, and extensive involvement of the chest wall at the back, it has apparently retarded further progress. In such conditions as inoperable cancer of the bladder it has been

found useful to relieve pain and for the control of hemorrhage, thereby making the patient more comfortable and apparently retarding the progress, but without curing the individual.

We have experimented with selenium compounds from three different manufacturers. The one from which we have obtained the best results and which we are at present using is manufactured by E. C. Steinach, of this city, and can be obtained of Munsch, Protzmann & Co., 410 Madison Avenue, in the form of tablets, which, it is stated, contain one and one-half milligrams of colloidal selenium, with about one grain each of chloride of potassium and sulphate of potassium. They also prepare the solution of potassium seleno-vanadate, as well as some of the salts of tellurium. Selenium is fortunately an inexpensive product to obtain, but the preparations should not, we have been informed, be manufactured from selenium that has been heated to a great extent, and care should be used to free the metal in the process of manufacture from all impurities.

Tellurium, like selenium, has the property of oxidation in the animal organism. It belongs to the same group as sulphur and se-

lenium. Its action is somewhat milder, and it therefore has to be given in much larger doses. Its toxic effects are much less than in the case of selenium, but they are harder to detect after the system is saturated, unless by chemical tests of the urine. It is an oxidizer, the same as selenium, and is recommended in cases where the neutral sulphur is present to a very great extent.

This is a much rarer element than selenium. The metallic tellurium at the present time upon the market varies anywhere from 20 per cent to 75 per cent to 95 per cent balance impurities; and while the salts are more stable than those of selenium, they are more difficult to prepare, tellurium being a less active element. It combines with the earthy elements like potassium, sodium lithium, to form soluble salts, which can be obtained in a reasonably pure state.

Tellurous acid salts have been given in five-milligram doses three times daily. Personally we have had no experience with its internal administration, but when taken to any considerable extent it sometimes produces a dermatitis, which fact renders the therapeutic use of tellurium valueless. In carcinomatous conditions tellurium may be best

employed as telluric acid, applied locally in an antiseptic solution. (See chapter on Antiseptics.)

Every tumor ought to be removed surgically if suspected to be malignant. Investigation of the urine as regards sulphur should be made previous to operation. The surgical removal of the tumor should also be followed by selenium administration. The success of the procedure surgically and the internal administration of selenium cannot be judged until some two or three years following the operation. However, if a recurrence follows in the old scar or as a result of metastases, this cannot be readily detected by a disturbance in the sulphur excretion.

CHAPTER VI

Preparations for Cleansing, Deodorizing, and Disinfecting Cancerous Lesions of the Skin

Practically all who have been in attendance on those suffering from ulcerated surfaces of the skin associated with cancer, if the ulceration was of any extent, have felt the need of some application that would place the ulcerated areas in a more healthul condition, and at the same time disguise or remove the unpleasant odor associated with them, a preparation not intended to act as an active destructive agent, like arsenous acid paste, previously mentioned, radium, X-ray, or excision; but for the purpose mentioned above we recommend Dakin's solution as prepared by Killian's formula, or the paste dichloramine T. The formulas for the manufacture of both these preparations are presented in this chapter. The medical profession is indebted to Dr. Alexis Carrel for work done, both abroad and at the Rockefeller In-

stitute, for popularizing Dakin's solution. Before giving these formulas it may be well to review briefly what action it is desired to obtain by their use, and the reasons for the same.

Nature has two defenses against infection. The first, the number of antibodies normally present or developed; and second, phagocytosis assisted by opsonins. These are the precise periods to remove infection. The antibodies start in from one to two hours from the period of contamination, up to twelve hours. The phagocytosis begins when the line of demarcation has been established between healthy and diseased tissue, and lasts for a longer period of time. The first thing to be done is to remove the necrosed tissue, because it is at this time that antiseptics find their greatest usefulness. The most common antiseptic used is carbolic acid (crude), introduced by Lister. Its power of asepsis is good, but it also destroys tissue.

In the cancerous ulcerations the period of contamination has passed before the patient comes under our observation. The proper preparation to be used is one which contains some of the qualities of a germicide (which destroys micro-organisms), of an antiseptic

(which works against sepsis), or of a disinfectant (which is used to combat infection, or to do away with it). The antiseptics are divided into: (1) phenolic; (2) metallic salts, $HgCl_2$, $HgNO_3$; (3) dyes; (4) halogens, *e. g.*, iodine, etc.; (5) miscellaneous, *e. g.*, hydrogen peroxide, alcohol, etc. Of all these the chlorine group has given the greatest satisfaction.

Chlorine Compounds.—There are four available chlorine compounds, of which two at present are widely employed. All of the chlorine compounds have chlorine in active form, loosely bound and readily given up. Attention is called to the fact that the principal test of chlorine is the liberation of iodine from KI. Some of the formulas are as follows:

Chlorine { chloramines / hypochlorite

Chlorine united to N

In studying the action of hypochlorites upon protein substances, H was replaced by chlorine, forming chloramino-acids. Chlor-

amino-acids are antiseptics. The principal hypochlorite preparations are Dakin's solution and eusol. To prepare eusol, bleaching powder and boric acid in equal parts are taken, water added, and filtered. These solutions make an alkaline mixture. $Ca(OH)_2$ and carbonate and $Ca(OCl)_2$ and a little HClO. These are very easily prepared. Formula for eusol:

12.5 gms. $Ca(OCl)_2$
12.5 gms. boric acid
1,000 c.c. water.

Dakin's solution must be neutral; 0.5 per cent NaOCl. When used in a stronger solution causes irritation, and below this is inefficient. Methods of making solution:

1. $Na_2CO_3 + Cl_2$ (gas).
2. $Ca(OCl)_2 + Na_2CO_3 + NaHCO_3$.
3. NaOCl + (from $Ca(OCl)_2$ with Na_2CO_3) boric acid.

The last of these three is the best.

Boric acid as a polybasic acid is more efficient in the neutralization of antiseptics than neutralization with sodium carbonate. In the preparation of an antiseptic we must get our

measure at a point where it gives a red color with alcoholic phenolphthalein, and no color with solid phenolphthalein. If it becomes too alkaline it destroys not only necrosed tissue, but also healthy tissue, and consequently hampers the neighboring tissue cells in their protective action against the invasion of any infection. On the other hand, if it is not sufficiently alkaline, its keeping properties are so very poor that it deteriorates two hours after preparation.

In the action of antiseptics on necrosed tissue the chlorine combines with the nitrogen, forming chloramino-acids. Consequently the mixture takes on an acid reaction, but the alkalinity of the antiseptic will neutralize this acid. In certain types of infection, and this is particularly true of those concerned in cancer, the mixture is more likely to become alkaline, and we must therefore have some compound in the antiseptic capable of neutralizing that alkalinity. For that purpose we have chosen as a substitute for boric acid, telluric acid. Telluric acid belongs to the same chemical group as boric acid, and it is likewise a polybasic acid. It therefore, like the phosphates and carbonates of the blood, has a true buffer action, covering a wide

range of hydrogen ion concentration. Moreover, telluric acid, or the salts of telluric acid, when used in moderate quantities, stimulate epithelial cells in their protective action against infection or the invasion of malignant cells. For the making of the antiseptic we follow the formula for Dakin's solution, where the sodium hypochlorite is prepared from chlorinated lime and sodium carbonate. This is rendered alkaline to phenolphthalein, and then telluric acid is added until the mixture gives no color with solid phenolphthalein. This requires very little telluric acid, and the keeping properties of the mixture are very good.

Application of the Antiseptic

To obtain the best results with the antiseptic, the wound is saturated every two hours, and between applications smears are made of the exudate. The smears are stained with Loeffler's menthylene blue, and the bacteria to a high-power field counted. The average of some ten fields is taken as a safe indication of the degree of infection. The antiseptic is applied until the number of bacteria is greatly diminished, that is, to one or two to a high-

power field. It will be noted at this period that the amount of exudate is very small. The wound, moreover, has taken on a healthier appearance and the invasion of neighboring parts has stopped. In some cases, as, for instance, in carcinoma of the breast, the application of the antiseptic continually may cause irritation. In that case it is wise to dilute it with an equal quantity of distilled water and apply more frequently. It is also to be recommended that if the antiseptic is to be kept for any length of time, that potassium permanganate be added, to the amount of 5 milligrams to a liter, to add to its keeping qualities. If a paste is desired, and in some cases, as in epitheliomata of the face, where constant irrigation without injury to other structures, as the eye, is impossible, the most valuable paste is that prepared by adding to sodium stearate dichloramine T, plus sodium arsenite. Dichloramine T may be made from sodium sulphonamide by adding hypochlorous acid, or preferably by adding to the sulphonamide sodium hypochlorite and heating until the solution is obtained, then adding acetic acid. A white crystalline precipitate is obtained, and this is taken up in the stearate as a vehicle and the arsenic is added. One gram

of the arsenite is added to 100 grams of the dichloramine paste. One application of this paste in twenty-four hours is sufficient. Unless some unforeseen condition should prevent, when using it, the Dakin's solution should be kept constantly applied by means of the tube, placed in the dressing in the manner in which it is ordinarily used. After the ulceration has been put into a healthy state, as mentioned above, then the wet dressing can be removed, and probably the washing off of the ulceration once a day through a glass syringe will be enough to keep it in a healthy state. Particularly in cold weather, it may be enough for such conditions as cancer of the breast, when it is not advisable or convenient for the patient to be confined to bed, to apply the paste instead of the solution once a day after the ulceration has reached a healthy state. In summer, on account of the tendency of the stearate to decompose, the paste had better not be applied over any extensive surfaces. The disagreeable odor will be disguised by the chlorine present in the Dakin's solution, and after the ulceration has reached a more healthy state, will cease of its own accord to be present, as the conditions which give rise to it will have been removed.

The above two preparations we recommend more highly than any other as the best local applications for cleansing, deodorizing, and disinfecting these ulcerated cancerous surfaces, but even where their action is attended with pleasing results, too much reliance should not be placed on them alone, but every endeavor should be made, through the internal administration of selenium or whatever medicinal preparations may be used, to take advantage of this opportunity to combat the disease by their internal administration and to use every other climatic and hygienic measure which is at the command of the attendant.

The formula for eusol is given in this chapter because it is easier to prepare than Dakin's solution and can be used in place of it when the latter is unobtainable. Where it is impracticable or impossible to employ all of the technique which we recommend as associated with the application of Dakin's solution, such as the examination of the smears under a high-power microscope, the attendant can use the preparations recommended, if found to be of benefit, according to his best judgment. Naturally it is easier to use these preparations in institutions which are properly equipped for pathological and chemical work. Unfor-

tunately, even to-day not infrequently institutions, otherwise well equipped for the care of individuals suffering from malignant disease, are very poorly fitted out in the above two particulars. Every two hours is sufficient to apply the solution through the tube. In this manner the dressing of gauze is kept constantly wet.

In cases where, in spite of all possible care, the application of Dakin's solution or the paste is found to disagree, there are, as previously mentioned, a great variety of antiseptic solutions or unirritating ointments that may be applied for the same purpose. Our experience has been that ordinarily the best results are obtained by the weak and less irritating germicides; solutions of aluminum acetate or lead and opium wash are sometimes useful. Boric ointment or an ointment which is at present on the market which contains tellurium and selenium, under the name of Unguentum Sel-Van-Sen, may be tried around the edges for the purpose of preventing further infection and with the idea of absorption of the selenium by the system.

The Dakin solution, modified according to the Killian formula, either plain or diluted, can be used, and its effects observed, on can-

cerous ulcerations on mucous membranes, either as a douche or a wash. Great care should be used, however, in using this solution around the face where there is an opportunity of its being inhaled, as the chlorine might prove irritating to the lungs.

CHAPTER VII

General Considerations

As has been stated, this little work is the combined efforts of a chemist and surgeon working together, both of whom have studied the cancer problem from their respective standpoints for several years. Some of the conclusions which have been presented are the result of the work that both of them have done, in association with homes for the relief of incurables, or as a result of observations made in hospitals, in the wards of which the most far advanced cases are apt to present themselves, being filled with the most dependent of all of a large city's population. Therefore, to a very great extent, the conclusions are founded on observations made on the most difficult cases. This work has intensified our belief in the value of what can be done for the relief of, or at least the retardation of the advance of the processes in earlier cases, when an accurate diagnosis has once been made, by the use of measures often

neglected, which we have at the present time, while expecting the discovery of some new remedial measure, possibly a serum, which will cure this condition in a semi-miraculous manner. We have learned not to expect too much from such preparations as tuberculin for tuberculosis, or from mercury or salvarsan in syphilis, although the use of these two latter have been of invaluable aid; and we should not expect too much from any sudden cure for cancer.

Just the same, in carcinoma we predicate that even now astonishingly good results can be obtained from the careful and persistent use of measures which we have at our command. The history taking is of the very greatest importance. In any case where there is the least ground to suspect malignant growth, in taking the history due regard must be paid to the fact that slow mental reaction follows questioning in many cases. It may be necessary to ask the same question over and over again, particularly concerning the cause of death of collateral relations of the individual who is being examined. Clinically such a condition has been observed by us as a marked increase of neutral sulphur in an individual of a distinguished family, where a

careful family history had been kept for one hundred years, and in whose family is recorded the death of eleven persons from cancer, the common ancestor being the patient's grandfather. In such individuals a careful history-recording will in time prove not only of aid in the diagnosis of any individual case, but continued careful history-taking will eventually help clear up some of the points in connection with heredity in this disease. Much still exists that can be accomplished in the future by observations of the records of the various countries, as shown by the report of the health officers, and the discovery of those regions where cancer does or does not exist. Our observations so far are that neither climatic conditions nor racial characteristics have any effect outside of the influence they may have on general hygienic conditions, but that heredity is a powerful factor which is always to be considered. Life in the open air, particularly for individuals in whom cancer is diagnosed in its earlier stages, cannot be too highly commended. Contrary to the opinion of many, we regard the question of diet of secondary importance, providing digestible food in sufficient quantities is obtainable. The diet can be modified somewhat

according to the exigencies in each individual case.

Everything should be done to cheer, encourage, and calm the mental state of unfortunate individuals so affected, and all measures of a material, social, and spiritual nature that are practical should be adopted for this purpose.

So far as we are able to ascertain, cancer differs from syphilis, in the earlier stages of the latter disease, in the fact that it is not contagious, and probably in that respect from tuberculosis also.

It is a question whether the somewhat complex question of cancer and marriage should be discussed in a work of this description, which is intended to be of a scientific character. It is desired to touch as little as possible on either philosophical or religious grounds. The three, however, are sometimes so dependent on one another that it is impossible to discuss them separately. Naturally, individuals of either sex with a malignant growth clearly demonstrable will refrain from marriage. It may be expected that an increasing number of individuals will be discovered as sufferers from a pre-cancerous state, either by the use of methods for diagnosis which are

just now commencing to be applied, or by increasing refinements in that direction from future discoveries. These people can probably be cured of a condition, when once it is recognized, by the careful adoption of every hygienic or medicinal measure calculated to increase and sustain proper tissue metamorphosis for at least two years. They can at least be relatively cured to the extent that individuals are relatively cured of other similar conditions, such as tuberculosis; and they probably will not transmit, to the extent they have received it, the tendency toward the development of malignant neoplasm. It is fair to hope that it is in accord with the laws of heredity (and apparently it is to the extent known to us) that through these measures it can eventually be bred out of the system, just as now, if we can go by the records that are already being presented to us, it is being bred in; and that in the future, and probably not far distant future, its frequency of occurrence will be very materially diminished.

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